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Electrophysiological evidence for long-axis intrinsic diversification of the hippocampus

Costas Papatheodoropoulos[1]

[1]*Laboratory of Physiology, Department of Medicine, University of Patras, 26 504 Rion, Patras, Greece*

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1. ABSTRACT

The elongated structure of the hippocampus is critically involved in brain functions of profound importance. The segregation of functions along the longitudinal (septotemporal or dorsoventral) axis of the hippocampus is a slowly developed concept and currently is a widely accepted idea. The segregation of neuroanatomical connections along the hippocampal long axis can provide a basis for the interpretation of the functional segregation. However, an emerging and growing body of data strongly suggests the existence of endogenous diversification in the properties of the local neural network along the long axis of the hippocampus. In particular, recent electrophysiological research provides compelling evidence demonstrating constitutively increased network excitability in the ventral hippocampus with important implications for the endogenous initiation and propagation of physiological hippocampal oscillations yet, under favorable conditions it can also drive the local network towards hyperexcitability. In addition, important specializations in the properties of dorsal and ventral hippocampal synapses may support an optimal signal processing that contributes to the effective execution of the distinct functional roles played by the two hippocampal segments.

2. INTRODUCTION

The hippocampus is an elongated brain structure that in rodents is roughly positioned in dorsal-ventral plane extending from the region of the septum to the medial temporal lobe (1) while in the human and other primates the hippocampus is positioned in the anterior-posterior plane of the brain (2). Thus, the longitudinal axis of the hippocampus is also known as the septotemporal or dorsoventral axis. The hippocampus is deeply implicated in forms of declarative memory (3–5), in spatial navigation (6–9) and also plays important roles in other brain functions including fear and anxiety (10–13) and sensorimotor processing (14, 15).

Scattered studies during the first periods of hippocampus research revealed the existence of some heterogeneity of function along the long axis of the hippocampus (16–18) as well as different anatomical and functional connectivity patterns between distinct segments along the hippocampal long axis with a first review appearing in 1959 (19). Following the concurrent demonstration of fundamental mnemonic functions attributed to hippocampus (20) a number of studies showed that the dorsal hippocampus is involved in some forms of spatial learning and memory more than the ventral hippocampus; for a review of these studies see (21). Currently, this kind of research has culminated in a rather general dichotomous view of hippocampus function; In particular that the dorsal hippocampus has a preferential involvement to cognition-related processes like spatial memory and navigation while the ventral hippocampus plays more important roles in emotion-related functions like fear and anxiety (10, 22, 23). The well established different extrinsic connectivity patterns of the dorsal and ventral hippocampus (24, 25) have dominated explanations of the functional segregation along the hippocampal long axis. However, several lines of early and recent research strongly suggest the existence of specialization in the local intrinsic neural network along the dorsoventral axis of the hippocampus providing evidence that extends from early electrophysiological observations on epileptiform activities (26, 27), to later neuroanatomical and neurochemical observations concerning the different levels of the various neurotransmitters and neuromodulators (many of them referenced in Strange *et al*., (23), to more recent evidence regarding fundamental population activities of the hippocampus (28–31).

This survey presents the early and recent electrophysiological evidence that suggests or directly demonstrates the existence of endogenous specializations along the long hippocampus axis. This review is focused on electrophysiology for several reasons. First, electrical activity of the neurons is the ultimate expression of their activity. Electrophysiological studies can provide information for most of the levels of neural organization, from the synaptic, to the single-cell, to the local circuitry level and can also provide evidence on basic properties of the neural circuitry such as cell and network excitability, neuronal synchronization and synaptic plasticity, the knowledge of which is necessary in order to understand signal processing in the network. Also, electrophysiological studies were among the first to show or to suggest that significant differences occur between the dorsal and the ventral hippocampus of experimental animals or the corresponding posterior and anterior hippocampus in humans. Electrophysiology has been used in comparative dorsal-ventral studies of the hippocampus for a wide range of purposes including the dissection of connectivity patterns, the study of epileptic/epileptiform activity, the study of physiological population activities, the single-cell properties, the study of behavioural outcomes of hippocampus stimulation and the study of synaptic plasticity. However, in this review the most pertinent evidence for the concept of intrinsic diversification will be presented and discussed.

The main aim of this review is to collectively present the current electrophysiological evidence that supports the notion of the intrinsic diversification along the dorsoventral axis of the hippocampus and to briefly discuss some possible implications. First, the presumed historical roots of the concept of functional segregation will be examined and the current views on this topic will be briefly described introducing the reader to the idea of endogenously organized diversification along the long axis of the hippocampus. Then, following a level approach, the electrophysiological evidence obtained for the physiologic and aberrant network activities, the synaptic transmission and synaptic plasticity as well as for the properties of single-cells will be presented. The implications of this evidence for the functioning of the local neural network on the dorsal and the ventral hippocampus will be tentatively discussed in a separate section while the possible future research directions will be described at the end of the article.

3. THE CONCEPT OF FUNCTIONAL DIVERSIFICATION ALONG THE LONG AXIS OF THE HIPPOCAMPUS

3.1. Historical background

The first ever study that detected differences in the tissue organization between the dorsal and the ventral hippocampus was published as early as 1944 by Nilges and colleagues (32). These authors, motivated by the selective vulnerability of the pyramidal cells of the CA hippocampal fields after carbon monoxide poisoning or epileptic activity, performed their study in six different species (opossum, guinea pig, rabbit, cat, dog and monkey) and found a richer vascularisation in the ventral than the dorsal hippocampus, an observation that has been confirmed and extended recently (33). More than a decade later Dunlop (34) using evoked potentials described that the vulnerability to carbon dioxide is lower in the ventral than in dorsal hippocampus. Although these findings have significant implications for the comparative susceptibility of the two hippocampal poles to ischemia and hypoxia only after several decades it was demonstrated the higher resistance of the ventral hippocampus to ischemia (35–37). Most of the following studies that revealed differences between the dorsal and ventral hippocampus concerned with the patterns of anatomical connectivity between the two segments of the hippocampus and other brain regions as well as with the epileptiform afterdischarges. Thus, from the eighteen studies detected and published until 1970,

seven of them investigated the connectivity patterns (26, 38–43) with six out of the seven studies using electrophysiology. During the same period were also published the first dorsoventral studies of epileptiform activity (26, 27, 41, 44) and of behavioural responses to selective stimulations or lesions of dorsal and ventral hippocampus (16–18, 45–49). Three studies were focused on physiological population activities (46, 47, 50) and one study detected neurochemical differences (51).

Already in the first studies it was emphasized the possibility of existence of significant functional diversification along the hippocampus or at least between its two extremities, the dorsal and the ventral poles. Thus, in 1960 Adey and colleagues (46) suggested that "It appears . that there is a considerable functional differentiation, both within the cell grouping at any one level and from different parts of the hippocampal arch as a whole". In the mid 1960s Elul (27) highlighted the fragmentary at that time nature of the evidence about possible regional differentiation of the hippocampus while a few years later Nadel (49) ascribed the failure of researchers to make a consistent picture of hippocampal function to the "observation that lesions in different regions of the hippocampus can produce quite different behavioral effects", and he noted that "differences between the dorsal and the ventral areas of the hippocampus have been demonstrated anatomically . and physiologically . and that they might differ in function as well". At the same period Brazier (50) suggested that "in terms of its electrophysiological characteristics, the hippocampus in man does not have uniformity throughout its length".

Despite these early suggestions, however, the first dorsoventral studies did not apparently succeed to appreciably influence the general perception of researchers for the homogeneity of the hippocampus. Thus, Adey and coll. (46) noted that "It has been widely assumed that a functional homogeneity characterized the hippocampus as a whole, presumably by reasons of its apparent structural homogeneity", and Elul highlighted the fact that the current prevailing view of the hippocampus was as a "uniform structure throughout its length". It is notable that even many years later Bragdon and colleagues (52) criticized the "tendency to regard the hippocampus as functionally homogeneous" which was "especially prevalent in studies related specifically to epilepsy" despite the fact that significant differences between the dorsal and the ventral hippocampus were already described. Thus, the idea of functional diversification along the long axis of the hippocampus developed rather slowly over time most probably because of the apparent homogeneity of the hippocampus at the macroscopic level as described above. Following early behavioural studies (16, 53, 54) comparative dorsoventral studies in the 1990s showed that the dorsal hippocampus is involved in spatial learning and memory more than the ventral hippocampus (21, 55–58). Early (39, 40, 43, 59, 60) and more recent evidence of distinct connectivity patterns of successive segments along the hippocampal longitudinal axis with other cortical and subcortical brain structures (24, 61–65) has provided strong mechanistic support to the concept of functional segregation along the dorsoventral axis of the hippocampus. Importantly, however, the different patterns of extrinsic anatomical connections are apparently accompanied by a vast repertoire of intrinsic specializations as presented and discussed in the following sections.

3.2. Intrinsic diversification

The distinction between extrinsic and intrinsic nature of dorsoventral differences was suggested even in the first studies, especially those that investigated and compared the evoked and spontaneous population discharges between the dorsal and the ventral hippocampus. For instance, Elul (27) implicitly pointed to intrinsic mechanisms to interpret the differences in the threshold and morphology of induced epileptiform discharges between the dorsal and the ventral hippocampus. However, more explicit reference to the possibility that intrinsic mechanisms may contribute to the observed dorsoventral differences was given in *in vitro* studies on the hippocampal slice preparation. For instance, the authors of one of the first *in vitro* studies proposed that intrinsic factors in the hippocampus may contribute to the gradient of increased frequency of spontaneous population epileptiform discharges observed in slices along the dorso-ventral axis (52). Similarly, a following *in vitro* study of electrophysiological responses (again epileptiform) recognized the possibility that the observed differences between the dorsal and ventral hippocampus may be intrinsic to the hippocampus (66). However, despite the rather convincing accumulation of data suggesting that several aspects of the intrinsic network display specialization along the dorsoventral axis of the hippocampus, apparently many researchers continue to thing about the hippocampus as an internally homogeneous structure. Thus, although the comparative behavioural studies has rendered the concept of functional segregation a rather established influential topic in the research of the hippocampus, the idea of intrinsic specialization has only very recently been treated with the attention it deserves. The reasons for this may be manifold. For instance, during the first comparative studies it became clear that consecutive segments of the hippocampus are differentially connected anatomically with other brain structures and consequent detailed anatomical studies provided strong evidence that the dorsal and the ventral hippocampus have distinct extrinsic connectivity patterns (see above section). The anatomical evidence can provide a reliable explanation of functional segregation along the hippocampus long axis.

It is important to note the hippocampus has been traditionally viewed as a homogeneous structure not only macroscopically (as described above) but also at the level of its endogenous organization. In early 1970s Per Andersen and his co-workers (67–69) elegantly demonstrated using *in vivo* electrophysiology that the excitatory activity in the hippocampus flows across a "trisynaptic circuit", which is the basis for the organization of independent slice shaped micro-modules repeated in a parallel "lamellar" fashion along the longitudinal axis of the hippocampus. Although Andersen and coll. recognized the existence and possible consequences of the longitudinal excitatory and inhibitory connections, firstly noted by Lorente De No (70), their work apparently led to a strong impression of internal homogeneity along the hippocampus. Additionally, it also suggested that the physiology of the hippocampus can be studied in the *in vitro* slice preparation. The idea that the basic circuit of the hippocampus can be contained in a lamellar piece of tissue and can function as a relatively autonomous module, in combination with the previously invented acute brain slicing method (71, 72) fuelled an explosive development in the basic electrophysiological research of the hippocampus (73–75). Thus, the psychological impact of unprecedented potentiality offered by the hippocampal slice preparation apparently covered the importance of longitudinal anatomo-functional peculiarities and contributed to a significant degree in neglecting inter-slice differences. Accordingly, the apparent homogeneity of the hippocampus was so influential that became a permanent implicit assumption during the consequent hippocampus research. Evidently, under these conceptual conditions only a few researchers remembered of the differences already found between consecutive segments of the hippocampus and even fewer were interested to study them. Certainly, the "lamellar" view of the internal structure of the hippocampus is the fundamental basis for perceiving the hippocampus internal organization and working on it albeit with some necessary adaptations (76, 77). Nowadays, as described in the following sections, there is a continuously growing body of evidence showing that many aspects in the fine organization of the hippocampus appear to be differentiated or specialized along the long axis of the "lamellar" hippocampus. The evidence comes from all levels of organization of the local hippocampal circuitry, from the level of gene expression (22, 78, 79) to the level of emergent, collective oscillations (28–31).

Here, it would be noted that the hippocampal slice preparation because of its isolation from the activities of other brain regions and the elimination of intra-hippocampal influences through the longitudinal anatomical connections can accurately provide evidence on the intrinsic specialization of the local neural network along the dorsoventral axis of the hippocampus. Thus, the hippocampal lamella, which obviously contributed to the idea of internal homogeneity, can on the other hand, pave the way for a more systematic study of endogenous heterogeneity along the hippocampal long axis. Obviously, the knowledge of the relevance of the hippocampal intrinsic specializations to the emergent functional diversification along the hippocampus requires the understanding of how these specializations lead to specific functional outcomes. Similarly, intrinsic cannot be completely separated from the extrinsic diversification. For example, a different innervation pattern of the dorsal and the ventral hippocampus from brain stem nuclei will be expectedly accompanied by a similarly diversified pattern of neurotransmitter receptor distribution. However, any difference in the structure and cellular actions of these receptors between the dorsal and ventral hippocampus should be categorized as a sign of endogenous specialization. Therefore, the endogenous diversification is intimately related with the extrinsic connectivity patterns of the hippocampus and emphasis should be given to the specific contributions of the different levels of neural organization to the functional segregation at the behavioural level.

4. NETWORK ACTIVITIES

4.1. Physiological rhythms

The dominant electrical activity patterns of the hippocampal circuit that appear in the local field potential signal are the theta rhythm, the sharp wave and ripples complexes and the gamma oscillation, which display characteristic frequencies, occur at specific behavioural states, are generated by different mechanisms and they are thought to play distinct functional roles in hippocampal signal processing (80–82). Briefly, the most widely assumed functions for these rhythms are as follows: a) the theta rhythm is engaged in coordination of multimodal sensory information and encoding of new information associated with exploration-related behaviours; also a putative role for theta is in memory consolidation during REM sleep (82, 83). b) SPW-Rs appear to be fundamentally involved in the mnemonic processes of stabilization and long-term consolidation of information (84–88), and they also appear to play important roles in the processes of memory-driven future planning (89–91) and decision making (92). The function of gamma oscillation is much less clear although it may be engaged in the encoding of current sensory information (93).

The first observation that a physiological population activity differs between the dorsal and the ventral hippocampus was made as early as 1960 by Adey and colleagues (46). These authors showed that trains of slow waves at 5–6 Hz (i.e. theta waves) that emerge in the hippocampus during a

goal-directed approach locomotor task were rapidly restricted on successive trials to the region of the dorsal hippocampus while they disappeared from the ventral hippocampus where the discharge reverted to a random irregular mode of generation with a slower component at ~4 Hz. At that time, Paul MacLean had observed rhythmic slow activity (perhaps theta) in the dorsal but not in the ventral hippocampus during exploration and during response to novel stimuli (94). A few years later in a systematic review M. Jouvet (95) described that the theta rhythm (4–4.5. Hz) can be regularly recorded in the dorsal but only occasionally in the ventral hippocampus during intense arousal in the cat. Then, in a study made in epileptic patients, Brazier (50) described that the anterior hippocampus (that corresponds to the ventral hippocampus in rodents) of the normal or less abnormal hemisphere displayed a higher ability for generation of spontaneous network activity while the posterior hippocampus was characterized by poor potentiality for electrogenesis. This conclusion was based on the observed excess of delta activity (2–4 Hz) in the most anterior part of the hippocampus and a prominent theta activity (6 Hz) in the middle zone of the hippocampus. Despite the fact that dorsoventral differences in theta activity were detected early, only recently the properties of the theta oscillation have been studied more systematically with respect to the longitudinal axis of the hippocampus. In an vitro study made on a whole hippocampus preparation Goutagny and colleagues (31) showed that although the theta oscillation can be simultaneously generated along a large extension of the dorsoventral axis the dorsal hippocampus appears to be entraining the ventral hippocampus since functional disconnection of the two hippocampal segments leads to a slowing of the theta oscillation in the ventral hippocampus. Also Lubenov and Siapas (96) have recently demonstrated that the phase of theta oscillation changes systematically along the dorsal third of the hippocampus of freely behaving rats comparing thus the theta oscillations as travelling waves preferentially propagating along the dorsoventral direction. Furthermore, recent studies by Chrobak and colleagues and Buzsaki and colleagues have shown that different features of the theta oscillation are more pronounced in the dorsal than in the ventral hippocampus. For instance, the theta rhythm power is higher in dorsal than in ventral hippocampus (97, 98); for a review, see (28). These differences between the dorsal and the ventral hippocampus may in part be accounted for by a different intrinsic organization of the hippocampal network along the septotemporal axis.

The other main network activity of the hippocampus is the complex activity of sharp waves and ripple oscillation (sharp wave-ripples, SPW-Rs) (82, 88), formerly named large irregular amplitude activity (LIA) (99). SPW-Rs occur mainly during consummatory behaviours characterized by tranquil alertness (88, 100). SPW-Rs represent a default pattern of the hippocampus since it is self-organized by the hippocampus when disconnected by its extrinsic inputs (101, 102) and it is also spontaneously generated in isolated hippocampal preparations under normal conditions (103–109). The particularly interesting recent observation that neurons that are activated in the intact animal during exploration are later reactivated during SPWs that occur spontaneously in hippocampal slices *in vitro* (110) further corroborates the idea that SPW-Rs is a basic default activity pattern of the hippocampus. The intrinsic emergence of SPW-Rs suggests that they may are implicated in memory retrieval (111) and also in imagery and future planning (89–91). An early hint for some difference in the generation of sharp waves between the dorsal and the ventral hippocampus may be the observation made by Adey and colleagues (46), several years before the first description of this activity (99) and its more systematic characterization (100, 112), that irregular slow waves of high amplitude at 2–4 Hz occurred mainly in the ventral hippocampus of immature cat.

Another recent *in vitro* study reported markedly different modes of generation of SPW-Rs between ventral and dorsal hippocampal slices (30). In particular, it was found that SPW-Rs are larger and they are generated at a considerably higher rate in ventral than in dorsal hippocampal slices. In addition, the frequency of the ripple oscillation is increased in the ventral hippocampus. The observation of increased likelihood of generation of SPW-Rs in the ventral hippocampus is corroborated by a recent *in vivo* study performed by Patel and his colleagues (29) who showed that although SPW-Rs can be initiated at any site of the hippocampus, however, SPW-Rs that are locally generated in the ventral hippocampus often remain isolated; In addition, the ripple oscillation propagated in the ventral-dorsal direction with a quasi two-fold higher probability compared with the dorsal-ventral direction. Also, SPWs in the intact hippocampus *in vitro* preparation from immature animals start in the ventral hippocampus and then propagate toward the dorsal hippocampus (108) presumably due to a dominance in coupling strength in the ventral-dorsal direction and a stronger inhibition along the ventral-dorsal direction as predicted in a model study (113).

An important observation made in the study of SPW-Rs in hippocampal slices was that the generation of SPW-Rs in multiple consecutive events forming clusters was much more frequent in ventral than in dorsal hippocampus (30). Remarkably, consecutive events in clusters occurred at a frequency of ~10 Hz in ventral but at ~5 Hz in dorsal hippocampus. Several lines of evidence suggest that clusters is an important feature of SPW-Rs. Clusters is a frequent mode of SPW-Rs occurrence in intact animals (89, 90), they require the activity of NMDARs (103) and they are

long-term potentiated following physiologically relevant pattern of presynaptic activation (103). In addition, the events inside the clusters occur at a pace (30, 103) that can lead to long-term synaptic modifications in the local network (114). Also, the multiunit activity that accompanies SPW-Rs occur at about two milliseconds earlier in dorsal than in ventral hippocampus. This difference in the timing of cell firing with respect to the network oscillation may have important impact on synaptic plasticity (115). Because clusters of SPW-Rs typically occur also in isolated hippocampal slices (103, 116) it has been speculated that clusters may represent an endogenous default mode of SPW-Rs generation that can provide the basis for organizing patterns of activity independently of the actual current behavior (117). This conforms to the suggested role of SPW-Rs in imaging not-yet experienced events (89–91) and is consistent with the proposed role of the hippocampus in episodic future thinking (118–121). It is therefore proposed that the ventral hippocampus dominate the endogenous initiation of SPW-Rs in the hippocampus and that the different pace of SPW-Rs inside clusters may reflect local requirements for optimal induction of synaptic plasticity in the two hippocampal segments (30).

4.2. Epileptiform activity

If memory is the first concept that is associated with (normal) hippocampus function, the second one is most probably epilepsy, a prominent pathological attribute of the hippocampus. Indeed, early observations showed that the hippocampus is the brain region most susceptible to epileptic activity displaying a particularly low threshold for the generation of seizure discharges (122–126). Subsequent *in vitro* experimentation in brain slices showed that epileptiform discharges were generated much more easily in hippocampal than other brain preparations (127). Thus, it is well established that the hippocampus plays a central role in the pathophysiology of temporal lobe epilepsy the most common type of epilepsy (128, 129). Furthermore, on the basis of accumulated, mainly experimental, observations it is now widely assumed that the ventral hippocampus in rodents and other experimental species is the most vulnerable segment of the structure to epileptiform discharges. Likewise, in epileptic patients the seizures most often start on the anterior hippocampus (that corresponds to the ventral hippocampus in rodents), which is the most affected area of the structure (130–132). The first comparative studies that reported differences in the pattern of epileptiform discharges between the dorsal and the ventral hippocampus were made on cats in the early 1960s (26, 27). Ironically, the conclusion that can be drawn from these early studies, with respect to threshold stimulation for the induction of discharges and the discharge frequency, is that the dorsal rather than the ventral hippocampus is more prone to epileptiform activity. The observations from another contemporary study that was also performed on cats (44) do not permit a safe conclusion on this matter. For the purpose of this review, a systematic search of the literature yielded thirty two studies that provide evidence on the generation of epileptiform activities comparatively between the dorsal and the ventral hippocampus or along the longitudinal axis of the hippocampus. Apart of the first three studies that were made on cats, the vast majority of both *in vivo* and *in vitro* studies (contributing equally) were conducted on rats (25 studies) and only four studies were made on mice.

Different experimental methods have been used for the induction of epileptiform activity, which were generally based on intense electrical stimulation, on altered ionic composition of the perfusion medium (in *in vitro* preparations) or on intervention to excitatory or inhibitory neurotransmission while some approaches used a combination of the above mentioned methods. Virtually, the *in vivo* studies followed the methodology of stimulation including the kindling model, the kainic acid model and the photostimulation. All the other models of induction of epileptiform activity were applied to *in vitro* hippocampal preparations. Five criteria were used to draw conclusions on the relative excitability of the intrinsic neural network along the dorsoventral axis of the hippocampus: (a) the site of spontaneous activity initiation, (b) the probability of activity emergence from a particular location, (c) the stimulation threshold required for the induction of epileptiform activity, (d) the rate of occurrence and finally (e) the duration or intensity of epileptiform activity. The spontaneous initiation of epileptiform activity can be studied either *in vivo* or *in vitro*. However, because epileptiform activity in the *in vivo* approaches typically starts at the site of stimulation, conclusions about the site of spontaneous initiation of epileptiform activity were drawn from *in vitro* studies that used the intact hippocampus or a longitudinal hippocampal slice. Thee of these studies reported that the preferred site of epileptiform activity initiation was the ventral hippocampus as observed in the disinhibited longitudinal slice that contained only the CA3 field (133) and in the whole hippocampus preparation from immature rodents in which epileptiform activity was induced either by low magnesium/high potassium concentration in the perfusion medium (134, 135) or by anoxia (136). However, the generation of epileptiform activity in the low Mg^{2+} model was ultimately (i.e. after establishment of the activity in the tissue) occurred first in the dorsal hippocampus and then propagated to the ventral hippocampus. In another study NMDA receptor-independent epileptiform activity induced by the blocker of potassium channels 4-aminopyridine in the neonatal rat whole hippocampus was generally initiated at the dorsal hippocampus, but sometimes the activity could start from either the dorsal or the ventral

hippocampus (137). More specifically, the preferable site of initiation of interictal-like bursts and tonic ictal-like discharges was the dorsal hippocampus while both the dorsal and the ventral hippocampus were potential sites of initiation of clonic ictal-like events. On the other hand, all the *in vitro* studies made on transverse hippocampal slices have unambiguously shown that the probability of emergence and/or the rate of occurrence or intensity of epileptiform activity are higher in the ventral than in dorsal hippocampal slices (52, 66, 138–144). Interestingly, the frequency of occurrence of epileptiform discharges increase gradually from the dorsal to the ventral hippocampus (52, 143) suggesting that the mechanisms underlying the increased network excitability change gradually along the dorsoventral axis. The *in vitro* electrophysiological studies performed either on slices or on the whole hippocampus preparation, provide the most homogeneous and compelling body of evidence demonstrates the relatively higher network excitability of the ventral hippocampus versus the dorsal hippocampus. Also, most of the *in vivo* studies concluded that the ventral hippocampus plays a dominant role on the initiation and/or the intensity of induced epileptiform activity (145–151). A typical parameter in the studies of epileptiform activity in the intact animal is the strength of the particular stimulation pattern that is required to trigger an epileptiform afterdischarge, i.e. the induction threshold (152), which can be considered as an index of the excitability of the local neural circuitry (153). Analyzing the relative literature it was surprising to find rather conflicting results on which of the two hippocampal segments shows the lower afterdischarge threshold. Thus, four studies have shown that the dorsal hippocampus displays the lower threshold (27, 154–156) while two other studies found lower threshold in the ventral hippocampus (145, 157). However, the kindling rate (i.e. the number of intermittent stimulations required before spontaneous epileptiform discharges are established) was most often found higher in the ventral than in the dorsal hippocampus (145, 149, 154), but in one study the kindling rate was higher in the dorsal hippocampus (155).

Regarding the propagation properties of the epileptiform activity along the longitudinal axis of the hippocampus, two *in vivo* studies have shown that afterdischarges preferentially spread along the ventral-dorsal direction (27, 158). Interestingly, one of these studies reported lower threshold for epileptiform activity induction in the dorsal hippocampus (27). In this study, seizures evoked in the ventral hippocampus propagated toward the dorsal hippocampus, which was readily activated, whereas the discharges evoked in the dorsal hippocampus propagated toward the ventral hippocampus very slowly and the ventral hippocampus was activated at an advanced stage of dorsal hippocampus seizures. The properties of propagation of epileptiform activity were also investigated in four *in vitro* studies using either the intact hippocampus preparation from immature animals (134–136) or the longitudinal CA3 slice preparation (133). In these studies the seizure-like activity induced in low Mg^{2+}/high K^+ medium (134, 135) or in the absence of synaptic inhibition (133) as well as the anoxia-induced depolarizations (136) initially originated in the ventral hippocampus and propagated dorsally. However, after the establishment of seizures in the whole hippocampus the seizures or the intra-seizure epileptiform events became bidirectional with the dorsal hippocampus playing a leading role (133–135). The bidirectionality was also the rule in a recent *in vivo* study that used photostimulation to trigger afterdischarges (159). Summarizing, the results from most of all studies on epileptiform activity including all *in vitro* studies converge to the idea that the ventral hippocampus is the most excitable segment of the hippocampus. This conclusion is principally based on evidence regarding the criteria of the site of spontaneous initiation, the likelihood of emergence and the rate of occurrence or the duration/intensity of epileptiform activity in the hippocampus. The evidence, however, regarding the direction of propagation of the established epileptiform activity along the longitudinal axis of the hippocampus is less homogeneous mainly pointing to a bidirectional spread of activity. The systems of longitudinal excitatory and inhibitory projections along the dorsoventral axis of the hippocampus (76, 160–164) may play an important role in the bidirectional propagation of activity (165). In addition, mechanisms of synaptic plasticity may contribute to the bidirectionality of propagation after the establishment of the epileptiform activity. For instance, epileptiform bursts initially generated in the ventral hippocampus and propagated along the hippocampus will drive activity at the dorsal hippocampus. This condition is favorable to trigger synaptic strengthening (166, 167) and establish epileptogenesis in the dorsal hippocampus (168). It is then expected that the potentiated synapses in the dorsal hippocampus will contribute to increasing local network excitability facilitating the local initiation of epileptiform discharges that can then be spread toward the ventral hippocampus.

5. SYNAPTIC FUNCTION

Although there is a plethora of neurochemical, neuroanatomical and behavioural comparative dorsoventral studies regarding the various neurotransmitters and neuromodulators the respective electrophysiological literature is rather limited and relatively recent. Most of the electrophysiological studies that provide comparative evidence on the excitatory and inhibitory synaptic transmission in the dorsal and ventral hippocampus have been performed on the CA1 field of transverse hippocampal slices using recordings of evoked and spontaneous activity and only a few

studies have been made on the dentate gyrus (DG) or the CA3 field. Major roles of the neurotransmitters and their receptors are their direct contribution to the mediation of the postsynaptic potentials, the regulation of neurotransmitter release, the control of neuronal excitability and the modulation of synaptic plasticity. Because of their significance to network functioning and the amount of observations currently available, the comparative findings regarding the excitatory and inhibitory transmission in the dorsal and the ventral hippocampus will be discussed separately.

5.1. Excitatory transmission

The excitatory synaptic transmission in the hippocampus, as in other brain regions, is mediated by the glutamate, which activates three types of ionotropic receptors, the AMPA, kainate and NMDA receptors (NMDARs) (169). Fast excitatory transmission in the hippocampus is primarily mediated by the AMPA and NMDARs, which are composed of different combinations of subunits (170), forming thus receptors with distinct functional properties. Glutamate also activates three groups of metabotropic receptors (mGluRs) (171), which can modulate the activity of hippocampal pyramidal neurons by acting at pre- and postsynaptic sites (172–175).

The excitatory transmission in the hippocampus is typically studied by electrically activating the afferent fibers in a particular dendritic area of the principal cells. In the CA1 field, stimulation of the Schaffer collaterals, which consist the projection of the CA3 to CA1pyramidal neurons (176) leads to the appearance of three different temporally consequent extracellular potentials: the presynaptic volley, which is the population action potential generated by the afferent fibers, the field excitatory postsynaptic potentials (fEPSP), and when postsynaptic depolarization is enough to cause neurons to fire the extracellular summation of synchronous action potentials gives rise to a population spike (PS). The fiber volley has been generally found similar between the dorsal and the ventral hippocampus (177–181). The fEPSP is consisted of an early fast rising phase and a late slowly decaying phase. The two components are based on partially different mechanisms and can be quantified by different measurements. Thus, non-NMDARs underlie the early fast phase of fEPSP (182), which is a measure of the number of activated synapses (183) and typically quantified by its maximal slope. Non-NMARs also participate to the late slower phase of fEPSP, which may also include the contribution of NMDARs that mediate a current with slow rise and decay times (184). The slow decaying phase of fEPSP can be quantified by the area of the fEPSP (185, 186). Most studies have shown that the basal synaptic effectiveness in the CA1 field, which is measured by the maximal slope of the rising phase of fEPSP evoked with stimulation of varying strength, is similar between the dorsal and the ventral hippocampus (177–179, 181, 187–192). Similar results have been obtained also when the fEPSP is measured with reference to the fiber volley (30, 178–180, 186, 188, 193). In contrast to the slope of fEPSP, the area of fEPSP evoked with moderate or strong stimulation strength and at a given value of the slope or fiber volley has been found greater in the ventral hippocampus than in dorsal hippocampus (186). The participation of NMDARs to the fEPSP evoked with relatively weak stimulation strength of the Schaffer collaterals under normal conditions is very small (194). However, under strong stimulation the postsynaptic depolarization produced by AMPA receptors is apparently enough to relief the magnesium block of the NMDARs channel leading to a appreciable contribution of these receptors to the fEPSP more in ventral than in dorsal hippocampus (186). The relatively increased ratio between NR2B and NR2A subunits of NMDARs in the ventral hippocampus (195) that confers a lower magnesium block of the NMDARs (196) and a prolonged decay of the NMDAR-mediated currents (197) may be a significant determinant for the increased participation of these receptors to the NMDAR-dependent evoked and spontaneous population activities in the ventral hippocampus (140, 143, 186). The distinct subunit composition of NMDARs in the ventral hippocampus may also contribute to the increased NMDAR-mediated epileptogenesis in the ventral hippocampus observed under blockade of adenosine A1 receptors (A_1Rs) (142). Interestingly, the NR2B subunit contributes to the spontaneous intrinsic generation of δ-frequency network activity recorded in the whole hippocampus *in vitro* significantly more at the ventral than the dorsal segment of the hippocampus (198). Also, intense exogenous activation of NMDARs produces a stronger suppression in the fEPSP in the ventral than in the dorsal hippocampus (188). Finally, as in CA1 field, the evoked synaptic potentials in the DG and the CA3 field are similar between the dorsal and the ventral hippocampus (199–201). Regarding neuronal firing, most of the studies have shown that the PS is fairly similar between the two hippocampal segments (30, 178, 188, 190, 202–204).

Excitatory synaptic transmission in the hippocampus as in other mammalian synapses depends on the release of neurotransmitter from the presynaptic terminal (205–207). The probability of transmitter release is a basic property of a synapse and is a function of the calcium entry from the extracellular space into the presynaptic terminal through voltage-dependent channels (208–210). Increasing or decreasing the extracellular concentration of calcium produces a corresponding change in the transmitter release and the postsynaptic response (211, 212). The calcium influx is antagonized by magnesium ions that block calcium channels, so increasing extracellular

magnesium concentration suppresses the transmitter release; the inverse result occurs when magnesium concentration is decreased (212). Remarkably, while the CA1 synapses in the dorsal hippocampus conforms very well to these rules the ventral synapses are insensitive to increases of extracellular calcium concentration (187) and to reduction in magnesium concentration (188). These observations can be interpreted by an increased probability of transmitter release in the ventral hippocampus. The probability of transmitter release directly impacts on phenomena of synaptic plasticity that depends on presynaptic mechanisms as it is synaptic facilitation (213) and observations on dorsoventral difference in synaptic facilitation provide further corroborative evidence for the increased probability of transmitter release in the ventral hippocampus (see section 5.3.).

In the hippocampus the release of the excitatory neurotransmitter glutamate is controlled by a number of presynaptic receptors (214). Among other receptors, adenosine A_1Rs (215, 216) and $GABA_B$Rs (217–219) powerfully control the release of glutamate in the hippocampus. Recently, it has been shown that also presynaptic cannabinoids CB1 receptors effectively control excitatory synaptic transmission in the hippocampus (220–222). An early study showed that exogenous activation of A_1Rs suppressed the evoked fEPSP in the CA1 field more in dorsal than in ventral hippocampal slices and that dorsal hippocampus had an increased number of A_1R binding sites (223). In addition, very recently has been shown that $GABA_B$Rs (179) and CB1 receptors (188) tonically control the excitatory synaptic transmission in the dorsal but not the ventral hippocampus. In addition to ionotropic receptors, glutamate activates also metabotropic receptors which comprise three groups of receptors (224). The metabotropic glutamate receptors type 5 (mGluR5) interact synergistically with NMDARs to potentiate the actions of the later (225) under the permissive control of adenosine A_{2A} receptors (A_{2A}Rs) (226). Accordingly, mGluR5 and A_{2A}Rs have excitatory effects on the hippocampus (175, 226–228). It has been recently shwon that under intense activation of NMDARs the excitatory effects of mGluR5 or A_{2A}Rs were absent in the ventral hippocampus although they were robust in the dorsal hippocampus (188).

5.2. Inhibitory transmission

The inhibitory synaptic actions in the hippocampus are mediated by the actions of γ-aminobutyric acid (GABA) on the $GABA_A$ and $GABA_B$ receptors (229). The $GABA_A$ receptors ($GABA_A$Rs) are heteropentameric ligand-gated chloride-ion channels formed by different subunit combinations that display distinct cellular localizations and functional properties (230, 231). $GABA_A$Rs located at synapses transiently inhibit the postsynaptic neuron through phasic actions while $GABA_A$Rs located at extrasynaptic sites are tonically activated by spillover GABA (232–234) to mediate prolonged changes in the membrane potential of the postsynaptic neuron (230, 235, 236). Both phasic and tonic GABAergic inhibition powerfully regulates the excitability in the hippocampus (237–239). Considering that $GABA_A$Rs play fundamental roles in the neural networks functioning (240) and are subject to extensive modulation by neuroactive substances (241, 242) it is expected that they will be the site of significant dorsoventral differences. For instance, the activity of mineralocorticosteroid receptors reduces the frequency of spontaneous IPSCs in ventral but not in dorsal hippocampus pyramidal cells (243). The function of $GABA_A$R is positively and strongly modulated by benzodiazepines, barbiturates and neurosteroids (241, 242, 244). It has been demonstrated that the barbiturates thiopental and pentobarbital and the neurosteroid anfaxalone enhance the strength and duration of $GABA_A$R-mediated inhibition in the CA1 field more in dorsal than in ventral hippocampus, but the enhancement of inhibition by benzodiazepines is similar in the two hippocampal segments (204). The subunit composition and the pharmacological properties of $GABA_A$R differ between the dorsal and the ventral hippocampus (245, 246). In particular, the relative expression profiles for the various subunits suggest that the prevailing types of $GABA_A$R in dorsal and ventral hippocampus are those containing the α1 and α2 subunit respectively (245). Interestingly, the expression of α5 subunit-containing $GABA_A$R (α5-$GABA_A$Rs) is higher in the ventral than in the dorsal hippocampus (245).

Regarding the $GABA_A$R-mediated postsynaptic actions, the effectiveness of both phasic and tonic inhibition appear to be different between the dorsal and the ventral hippocampus. The comparative study of the properties of $GABA_A$R-mediated inhibitory postsynaptic events is rather limited. The amplitude of $GABA_A$R-mediated spontaneous and evoked inhibitory postsynaptic currents (IPSCs) (243) and evoked inhibitory postsynaptic potentials (IPSPs) (202) is higher in the dorsal than in ventral hippocampus. The rise time of evoked IPSCs and the peak amplitude of IPSPs are similar in the two hippocampal segments (202, 243). The decay time of IPSCs has been found similar in dorsal and ventral hippocampus, however, the duration at half amplitude of IPSPs is twofold longer in dorsal than in ventral hippocampus (202). Also, the reversal potential of IPSP appears to be slightly more negative in dorsal than in ventral hippocampus (202). On the other hand, the frequency of miniature IPSCs (192) but not the spontaneous IPSCs (243) is higher in the ventral than in dorsal hippocampus. These observations provide a first look at the $GABA_A$R-mediated cellular actions in dorsal and ventral hippocampus leaving, however, a more comprehensive comparative study of these actions in the two hippocampal segments for the future. The

$GABA_A$R-mediated inhibitory actions on the local networks of dorsal and ventral hippocampus are more systematically studied (202–204). Thus, using the experimental paradigm of paired-pulse stimulation it has been shown that the $GABA_A$R-mediated recurrent inhibition in the CA1 field displays a twofold lower strength, a threefold faster decay and a more than twofold shorter duration in the ventral than in dorsal hippocampus (203). These differences may to some extent be attributed to the different $GABA_A$R subunit stoichiometry since the inhibitory currents mediated by $GABA_A$Rs that contain the α1 subunit, which dominates in the dorsal hippocampus, have increased amplitude (247). In contrast to the situation in the CA1 field, the $GABA_A$R-mediated recurrent inhibition in DG has been found stronger in ventral than in dorsal hippocampus while the inhibition in the CA3 field is similar in the two hippocampal segments (200). As mentioned, the α5-$GABA_A$R prevails in the ventral than in dorsal hippocampal CA1 field (245). The α5-$GABA_A$R is one of the most abundant subtypes of $GABA_A$Rs in the CA1 hippocampus field (248, 249) and is activated by relatively high levels of ambient GABA (250) to mediate tonic inhibition (237, 250). Taking into account that the levels of extracellular GABA are higher in the ventral than in the dorsal hippocampus (251) and that blockade of α5$GABA_A$Rs facilitates the induction of LTP in the ventral but not the dorsal hippocampus (178) it is tempting to speculate that the $GABA_A$R-mediated tonic inhibition is increased in the ventral hippocampus.

The $GABA_B$ receptors ($GABA_B$Rs) are G protein-coupled receptors located at postsynaptic and presynaptic sites. Postsynaptic $GABA_B$Rs by activating potassium channels produce membrane hyperpolarization and regulate membrane excitability while presynaptic $GABA_B$Rs regulate neurotransmitter release (252, 253). In addition, postsynaptic receptors directly modulate glutamate receptors (254). $GABA_B$ autoreceptors located on GABAergic terminals and $GABA_B$ heteroreceptors located on glutamatergic terminals regulate the release of GABA and glutamate respectively (219). Activation of $GABA_B$ autoreceptors during paired-pulse stimulation leads to a reduction in GABA release and postsynaptic inhibition facilitating the enhancement of the postsynaptic excitatory response (255–257). This $GABA_B$R-dependent action is more prominent when the inter-pulse interval is around 200 ms, i.e. the stimulation frequency is ~5 Hz, and strongly facilitates short-term and long-term potentiation of excitatory synapses (179, 185, 186, 258, 259). Both presynaptic (179, 186) and postsynaptic (143) $GABA_B$R-mediated actions appear to be stronger in the dorsal than in ventral CA1 hippocampal field.

5.3. Synaptic plasticity

Synaptic plasticity is the activity-dependent change in synaptic efficacy maintained over short or long periods of time (260, 261). Short-lasting and long-lasting changes in synaptic efficacy are thought to play fundamental roles in the processes of neural information processing and learning and memory (262, 263). Synaptic facilitation (also called paired-pulse facilitation) is among the simplest and shortest phenomena of synaptic plasticity observed when two stimuli are applied to presynaptic fibers in rapid succession (typically < 1 s). Facilitation consists of an enhancement of postsynaptic response caused by an increased transmitter release evoked by the second stimulus and it is therefore thought to be primarily based on presynaptic mechanisms (264). The excitatory CA1 synapses display considerably diverse properties including transmitter release probability (265) and facilitation/depression during consecutive activation (213). Furthermore, this heterogeneity can be observed even between synapses formed by a single neuron (266–269). It has been also concluded that most of the excitatory CA1 synapses release with low probability (266, 267, 269, 270). Expectedly, considering that the synaptic facilitation is inversely related to the probability of transmitter release (213, 271), the hippocampal synapses show substantial facilitation. However, this conclusion was drawn from studies of the dorsal hippocampus. Thus it was astonishing to observe the remarkably low facilitation shown by the ventral hippocampal synapses (187). Because the facilitation studied with field potential recordings represents a large population of synapses the observed dorsoventral difference in facilitation should not be influenced by a local heterogeneity in synaptic properties; rather it may indicate actual differences in the average probability of transmitter release between the dorsal and the ventral hippocampus. In addition, the higher degree of change of facilitation with decreasing calcium concentration in the ventral than in the dorsal hippocampus (187) is also consistent with the idea that synapses with high probability of transmitter release are more sensitive to conditions that reduce the release of transmitter (266). Interestingly, the facilitation at the CA3-CA3 and DG-CA3 synapses follows a similar pattern of dorsoventral difference, i.e. dorsal synapses display higher facilitation than ventral synapses (200, 201). Also the GABAergic synapses display higher facilitation in the dorsal than in the ventral hippocampus (192, 243). The observations on synaptic facilitation in combination with the insensitivity of the ventral CA1 synapses to manipulations that should increase synaptic responses have led to the hypothesis that ventral compared with dorsal synapses may have a higher basal probability of transmitter release (186, 187). However, the results of a recent study showed that the frequency of miniature excitatory postsynaptic currents and the activity-dependent inhibition of NMDAR-mediated currents by the channel non-competitive NMDAR antagonist MK-801 are similar in the dorsal and ventral CA1 synapses (193) suggesting that the

probability of transmitter release is the same at the dorsal and the ventral hippocampal synapses (266, 272). Nevertheless, another recent study showed that the frequency of miniature inhibitory postsynaptic currents is higher in the ventral than in the dorsal CA1 field suggesting that the probability of transmitter release is increased in the ventral hippocampus also at GABAergic synapses (192). Thus, it seems that although the large dorsoventral difference in synaptic facilitation is well documented (186–188, 192, 193, 201, 273) further studies are required in order to definitely conclude whether the transmitter release probability differs or not between the dorsal and the ventral hippocampus.

Another form of short-term synaptic plasticity is the response of a synapse during consecutive activation with more than two pulses delivered at a varying frequency. Under these conditions and when the number of pulses does not exceed a few decades the synapse reach a steady state of facilitation or depression. When the pulses are delivered to Schaffer collaterals at frequencies from 0.1. to 100 Hz, ventral CA1 synapses respond with a strikingly different mode compared with the dorsal synapses. Thus, dorsal synapses show facilitation from 1 to 40 Hz and afterwards are depressed while ventral synapses are steadily depressed at frequencies greater than 10 Hz showing only a small facilitation at 1 Hz (187). With a similar fashion, during the first few decades of consecutive pulses delivered at 5 Hz the dorsal and the ventral CA1 synapses show facilitation and depression respectively (193). Any dorsoventral difference in the machinery of neurotransmitter handling at the presynaptic terminal could contribute to the different response patterns displayed by the dorsal and the ventral synapses. For instance, the presynaptic Ca^{2+} sensor synaptotagmin VII is crucially involved in paired-pulse synaptic facilitation and frequency facilitation (274). Interestingly, the dorsal hippocampal synapses of mutant mice lacking the gene that encodes synaptotagmin VII show very reduced paired-pulse facilitation or frequency depression instead of frequency facilitation (193, 274) a situation that reminds the behaviour of the ventral hippocampus (187).

As abovementioned, the synaptic strength at excitatory synapses is typically measured by the slope of excitatory postsynaptic potential (EPSP) since it is linearly related to the number of activated synapses. Changes in the slope of fEPSP that occurs during phenomena of short-term plasticity are mediated almost exclusively by presynaptic mechanisms (264). However, synaptic plasticity can be induced also in the late phase of EPSP by both presynaptic and postsynaptic mechanisms. For instance, the facilitation of the area of fEPSP requires the activity of presynaptic $GABA_B$Rs, postsynaptic $GABA_A$Rs and NMDARs (186, 257, 275). By virtue of their different underlying mechanisms the fast and slow components of EPSP signal different frequency domains of the presynaptic activity. Thus, facilitation of the slope of EPSP appears to be more suited to signal inputs of relatively high frequency while facilitation of the late phase of EPSP more reliably codifies slower inputs providing optimal input gain for frequencies around 3–7 Hz (185, 186, 257, 276) which falls into the frequency range of the theta rhythm in the hippocampus (277). The dorsal and the ventral hippocampal synapses display markedly different paired-pulse facilitation of the late phase of fEPSP induced at inter-pulse intervals that correspond to the frequency of theta rhythm (186). Thus, the late component of fEPSP is optimally facilitated with paired-pulse stimulation at theta frequency (5 Hz) in the dorsal but not the ventral hippocampus (186).

Among the many forms of synaptic plasticity n the hippocampus (278) long-term potentiation (LTP) has attracted the interest of researchers since it appears to serve as a primary experimental model to study the basic mechanisms of learning and memory (279–281). Accordingly, LTP has been extensively studied in the hippocampus and especially at the synapses between the CA3 and CA1 pyramidal cells (more than 50% of all published studies on hippocampal LTP are performed in CA1; based on a PubMed survey). Until recently, however, virtually all studies on LTP in the hippocampus were performed on the dorsal part of the hippocampus. The first study that examined comparatively the LTP between the dorsal and the ventral hippocampus appeared in 2000. This study, conducted in the CA1 field of hippocampal slices showed that the classical high-frequency stimulation protocol that consisted of 100 pulses at 100 Hz and readily produces LTP in the dorsal hippocampal synapses induced a strikingly small-amplitude LTP in the ventral synapses (177). This dorsoventral difference was then confirmed with both *in vivo* (273) and *in vitro* experiments (106, 190, 192).

Higher magnitude of LTP in the dorsal compared with the ventral CA1 hippocampal field has been also found with lower (10 Hz) (178) or higher (200 Hz) than 100 Hz frequency of stimulation (189). It appears that with 10 Hz stimulation the activity of α5$GABA_A$Rs hampers the induction of LTP in the ventral hippocampus (178) while with 200 Hz the interaction of NMDARs with type-L calcium-dependent calcium channels (VDCC) is more effective in the dorsal hippocampus resulting in LTP of higher magnitude in the dorsal than in ventral hippocampus. Nevertheless, the LTP elicited with 200 Hz is maintained in both hippocampal segments for at least seven hours (189). The more physiologically relevant activity pattern of theta burst stimulation, which is known to reduce the activation threshold for LTP induction (258), also elicits NMDAR-dependent LTP more reliably in dorsal than in ventral CA1 synapses virtually through mechanisms

that lead to increased postsynaptic depolarization and excitability (179). Similar mechanisms appear to underlie the higher ability of the dorsal compared with the ventral hippocampus to show robust NMDAR-dependent LTP following 5-Hz stimulation (193).

Yet, in another recent study performed, however, in disinhibited slices the threshold for LTP induction has been found higher in dorsal CA1 neurons by virtue of activity of G protein-coupled inward-rectifying potassium channels (GIRKs) on dendritic excitability (282). The ability of the two hippocampal segments to undergo long-term synaptic changes appears to be modulated by corticosteroid receptors. Thus, acute stress or exogenous activation of membrane glucocorticoid receptors reduce LTP and increase long-term depression in the dorsal CA1 field while the opposite effects occur in the ventral hippocampus through activation of membrane mineralocorticoid receptors (180, 283). Interestingly, similar modulations of LTP in the dorsal and the ventral hippocampus of adult rats have been observed following juvenile stress and these effects were accompanied by a decrease in β-adrenergic receptor activity in the dorsal and a corresponding increase in the ventral hippocampus (284, 285). Furthermore, prenatal stress facilitates LTP in the ventral but not dorsal hippocampus (286).

The magnitude of VDCC-dependent LTP has been found higher in the CA3 field of the dorsal as compared with the ventral hippocampus (201). However, in the dentate gyrus of freely moving rats 200 Hz stimulation induces LTP of similar magnitude in the dorsal and intermediate hippocampus (199). Low frequency stimulation at 1 Hz does not induce any long-term change in the synaptic effectiveness either in the dorsal or the ventral CA1synapses in anesthetized rats (287) although it induces long-term depression in the dentate gyrus of the dorsal but not the intermediate hippocampus (199). Interestingly, however, low-frequency burst stimulation induces long-term depression more reliably in the ventral than in the dorsal CA1 field of anesthetized animals (287).

6. INTRINSIC CELL-PROPERTIES

Only recently the intrinsic cell properties have been studied comparatively in the dorsal and the ventral hippocampus. Several of these properties have been found to differ between dorsal and ventral CA1 pyramidal cells. There is no absolute consensus, but various observations suggest that the ventral CA1 pyramidal cells are more intrinsically excitable compared with their dorsal counterparts. This difference is attributed to dorsoventral differences in the morphological and physiological properties of the neurons. Thus, the ventral neurons have smaller dendritic length and surface area than the dorsal neurons (288, 289), but see also (290). More depolarized resting membrane potential in CA1 ventral than in dorsal pyramidal neurons has been found in three studies (288, 290, 291), but three other studies have reported no significant dorsoventral difference (193, 202, 243) and one study has reported that the ventral neurons have more hyperpolarized resting membrane potential (79). Similarly, some studies have shown higher input resistance in ventral compared with dorsal neurons (79, 192, 288, 290, 291) yet, other studies have reported no difference between dorsal and ventral neurons (193, 202) or increased input resistance in dorsal neurons (243). Furthermore, the threshold for action potential generation appears to be lower in ventral than in dorsal neurons (79, 243, 288), but see also (193). The after-depolarization appears similar in the two kinds of neurons (79, 193) and the after-hyperpolarization has been reported either similar (193) or larger in the ventral neurons (79). There is also a lower expression of A-type potassium channels in ventral than in dorsal hippocampus neurons (292) and M-type potassium channels, which also reduce excitability, are stronger in dorsal than in ventral neurons (291). In addition, the resting A_1R-mediated GIRK (potassium) conductance at the soma (293) and the apical dendrites (282) is lower in ventral than in dorsal pyramidal neurons and this may also contribute to increasing excitability in ventral neurons. The back propagation of action potentials is enhanced and the summation is decreased in the dendrites of the ventral hippocampus (292). Differences in other properties may confer different integrative properties to dendrites of dorsal and ventral hippocampal neurons. For instance, the amplitude and activation kinetics of the hyperpolarization-activated current (I_h) differ between dorsal and ventral neurons and the resonance properties differ accordingly (290, 292, 294), but see also (291).

7. PHYSIOLOGICAL IMPLICATIONS

7.1. Dorsal and ventral hippocampus: which is the most excitable?

Stricto sensu, excitability is the property of some cells to generate action potentials. This property is based on a number of basal ionic conductances in the cell membrane in combination with given extracellular and intracellular concentrations of respective ions. However, in a more physiologically meaningful way, the neuronal excitability, i.e. the excitability of a cell or intrinsic neuronal excitability, is determined by a plethora of ion channels in the cell membrane with diverse distribution, density and functional properties in combination with the particular structural characteristics of the neuron (295–297). The membrane ion channels influence neuronal excitability by controlling the impact of any synaptic input on the probability of action potential generation (182).

Accordingly, the intrinsic membrane conductances and excitability properties of a neuron shape the neuronal firing pattern translating in this way the synaptic input into a particular output of the neuron. Furthermore, neuronal excitability may have important implications for the network activity since single principal neurons in cortical circuits can drive the activity of the whole local population (298, 299). Actually, however, because neurons are integral constituents of the synaptic neural networks and their activity is meaningful only as components of these circuits, the excitatory and inhibitory synaptic inputs in a given neuron play an important role in determining the neuronal excitability. Therefore, the neuronal excitability can be perceived as a property that is dynamically determined by both intrinsic neuronal conductances and the synaptic inputs and can be called network-driven neuronal excitability. The synaptic activities, in addition to their implication in cell excitability, are also basic determinants of the excitability state of local neuronal circuits. The excitability of a local neural network is therefore determined by the relatively stable intrinsic excitability of the neuronal cells and the continuously changing synaptic activities (300). It would therefore be assumed that ultimately the excitability in working local neuronal networks is generally determined by a dynamic balance between synaptic excitation and inhibition (301). The dynamically and spatiotemporally controlled network excitability state modulates fundamental properties of local neuronal circuits including the degree of network responsiveness to inputs, the signal initiation and the propagation of the activity in the network (302).

As described above, several lines of evidence suggest that the local neuronal network of the ventral hippocampus is the more excitable segment of the structure. Historically, the idea of the increased excitability of the ventral hippocampus originated from early studies of temporal lobe epilepsy that showed a higher susceptibility of the anterior part of the human hippocampus to epileptiform discharges. This idea was further corroborated by subsequent *in vitro* studies carried out in hippocampal preparations (most often transverse slices) that showed that the ventral hippocampus generates epileptiform activity more readily than the dorsal hippocampus. In summary, direct evidence for the higher network excitability of the ventral hippocampus is provided by the observation that epileptiform activity starts or it is more intense in the ventral than in the dorsal hippocampus (52, 66, 133–136, 138–151) and it preferably propagates (at least at the beginning of its generation) along the ventral-dorsal direction (27, 134–136, 158). Furthermore, the ventral hippocampus is revealed as the favorable site of physiological rhythms generation as well. Thus, the activity of SPW-Rs, the generation of which requires increased excitability (110, 117, 303–306), is more readily generated in the ventral than in the dorsal hippocampus (30) and propagates preferably along the ventral-dorsal direction (29, 108). In addition, delta activity is more prominent in the anterior than in the posterior human hippocampus (50).

A number of mechanisms appear to contribute to the increased excitability of the ventral hippocampus. Most notably, the increased intrinsic excitability of principal cells (192, 288, 289, 291, 294), the reduced GABAergic inhibitory actions (143, 202–204, 243) and the reduced control of glutamate release by presynaptic receptors (179, 188, 223) may represent direct mechanisms underlying the increased excitability of the ventral hippocampus. Also, NMDARs may especially contribute to the hyperexcitability of the ventral hippocampus under favorable conditions such as low extracellular concentration of magnesium (134, 135, 140, 142, 143). Considering the activity of SPW-Rs, it should be noted that the mechanisms underlying its initiation in the hippocampus are unclear; what is clear, however, is that SPW-Rs is a self-organized endogenous activity of the hippocampus that does not requires input activity from other brain regions (307). Therefore, the mechanisms contributing to increased intrinsic excitability in the ventral hippocampus appears to be essential for the initiation of SPW-Rs.

During the previous discussion becomes apparent that ventral hippocampus is more excitable than dorsal hippocampus. The question then arises whether the increased network excitability of the ventral hippocampus plays a physiological role or it is a secondary effect of other functional requirements of the ventral hippocampus. It is argued that the higher tendency of the ventral (or anterior) hippocampus to organize physiological rhythms such as SPW-Rs in combination with the constitutively higher intrinsic neuronal excitability and the lower synaptic inhibition in this hippocampal segment strongly support the view of increased excitability being a basic property of the ventral hippocampus local network.

7.2. Stability in the ventral hippocampus

It is clear from the previous discussion that under physiological conditions the ventral hippocampus displays increased excitability, which is a basic network property that appears to importantly contribute to the ability of the ventral hippocampus to initiate the synchronous endogenous activity of SPW-Rs. However, under favorable conditions this property can drive the ventral hippocampus into a hyperexcitability state resulting in the generation of epileptiform population discharges. As a matter of fact, the physiological function in neuronal networks is based on the long-term maintenance of stable levels of activity that results from balanced excitatory and inhibitory synaptic actions on principal neurons (110, 308, 309) although the brain functional demands may require significant but transient local changes in excitability, as

for instance occur during the hippocampal activity of SPW-Rs. Interestingly, both SPW-Rs and epileptiform activity represent phenomena of increased neuronal synchronization and excitability (81, 310, 311) and SPW-Rs can indeed be transformed into pathological events (307, 312–314). This may occur in widespread shifts in the balance between excitation and inhibition (311). Under conditions of hyperexcitability the local neuronal circuitry fails to function normally and the information processing is impaired (309). Thus, a local neuronal network that continuously maintains an increased level of global excitability could not probably cope with its physiological functional demands and the ventral hippocampus could not be an exception. It is here emphasized that under normal conditions the ventral hippocampus obviously functions very effectively keeping the balance between excitation and inhibition in physiological levels. Considering the existence of endogenous network mechanisms that might underlie the tendency of the ventral hippocampus for hyperexcitability the requirements for long-term stability and normal function of the network suggest that other mechanisms may potentially act to balance this tendency of the ventral hippocampus.

As described in the section 6, the CA1 pyramidal cells appear to be more excitable in the ventral than in the dorsal segment of the hippocampus as observed with intracellular recordings (192, 243, 288, 289, 291–294). However, a recent study has shown that the extracellularly recorded complex spike bursting, the typical physiological mode of activity of hippocampal pyramidal cells (315–318), is more intense in the dorsal than in the ventral hippocampus (30). It should be noted here that the two experimental approaches to studying neuronal excitability provide different information. Intracellular studies require the experimental manipulation of the cell and give important and direct information about the intrinsic cell properties. On the other hand, extracellular recordings give the opportunity to study in an unmanipulated manner the spontaneous cell firing activity that is influenced by the intrinsic neuronal properties but is mainly determined by the background synaptic activities in the local network (319). Then, the relatively low background network-driven spontaneous cell activity in the ventral hippocampus may represent a homeostatic mechanism that regulates the basal network excitability by counteracting the increased inherent propensity of the ventral hippocampus network for hyperexcitability. Therefore, the low basal neuronal excitability in the ventral hippocampus, which may result from the action of homeostatic mechanisms in response to increased network activity (320), may be importantly implicated in the long-term stability of the local network contributing thus to the effective functioning of this part of the hippocampus.

Another mechanism that may potentially contribute to the long-term stability in the ventral hippocampus network is its relatively low ability for long-term synaptic potentiation. As described in the section 5.3., the ventral compared with the dorsal hippocampus displays higher induction threshold (178, 179) and lower magnitude (106, 177, 190, 273) of NMDAR-dependent LTP. Synaptic strengthening facilitates epileptogenesis (168) while keeping the LTP induction threshold low reduces the risk of uncontrolled excitation (278). Evidently this is especially important in circuits with relatively high endogenous excitability as it occurs with the ventral hippocampus. Homeostatic mechanisms in these networks may therefore work to keep the threshold high in order to assure network stability at an optimal level while preserving the necessary ability for plastic synaptic changes. It is important to note that long-term network stability can be achieved by alterations that occur not only at the level of synaptic interactions but also at the level of intrinsic cell properties that determine the intrinsic excitability of the neurons that impact synaptic plasticity (321) and some intrinsic conductances may contribute to decreasing excitability in ventral neurons. The induction of NMDAR-dependent LTP can be obviously regulated by mechanisms that target NMDARs. Interestingly, it has been recently demonstrated that the dorsoventral differences in NMDAR-dependent LTP involves an increased level of calcium-activated SK-type potassium channels that strongly restrict the activation of NMDARs in the ventral hippocampus reducing its ability for LTP (193). Importantly, the enhanced suppression of NMDARs by SK channels may decisively be implicated to limit burst firing in the ventral hippocampus (179, 193) and thus hamper the transition of this susceptible segment of the hippocampus towards hyperexcitability.

The inhibitory GABAergic transmission plays crucial roles in determining the degree of excitability and synchronization in cortical neuronal networks (322–324). As discussed above, in the CA1 field, which is the output of the hippocampal circuit, the $GABA_A$R-mediated phasic inhibition is weaker (178, 202, 203, 245) while the tonic inhibition appears to be stronger in the ventral than in the dorsal hippocampus. A consequence of the increased readiness of the ventral hippocampus for synchronized activities of its principal cells could be the strong recurrent activation of its GABAergic neurons (325, 326). Then, when groups of inhibitory cells are synchronously activated the amount of released GABA is increased (327) and it can spill outside the synapse to activate extrasynaptic $GABA_A$Rs, e.g. α5-$GABA_A$Rs which prevail in the ventral hippocampus (245), contributing in this way to the inhibition of the postsynaptic neuron (232, 328). Therefore, an increased tonic inhibition mediated by extrasynaptic α5-$GABA_A$Rs may act to compensate for the relatively low phasic inhibition in the ventral hippocampus and hence it may be a potential mechanism through which the ventral hippocampus can be protected against the risk of transition toward

a hyperexcitable state during periods of synchronous network activity (329). Interestingly, enhanced levels of extracellular GABA can downregulate phasic release and reduce the activity of presynaptic $GABA_B$Rs leading to an enhancement of tonic and a diminution of phasic activity (330). Similarly, it has been proposed that an increased tonic inhibition can lead to a reduction in phasic inhibition (331).

As described above, under conditions of intense activation of NMDARs there is a higher suppression in the excitatory synaptic transmission in the ventral than in the dorsal hippocampus and the potentiating actions of A_{2A}Rs and mGluR5 are present in the dorsal but not the ventral hippocampus (188). In addition, under blockade of A_1Rs, the A_2Rs appear to protect the ventral hippocampus from NMDAR-independent epileptogenesis (142). Thus, under conditions that endow the risk of runaway excitation, NMDARs, mGluR5 and A_{2A}Rs may act to dampen ventral hippocampus hyperexcitability. It is, however, noted that under normal conditions mGluR5 participate to the induction of LTP similarly in both dorsal and ventral hippocampus (179, 190). Therefore, it can be concluded that although some neurotransmitter receptors that control the excitatory glutamatergic synaptic transmission display reduced effects in the ventral hippocampus (namely A_1Rs, CB_1Rs and $GABA_B$Rs) other receptors (e.g. α5-$GABA_A$Rs, A_2Rs) can act to keep the network activity within a physiological range and thus hampering the tendency of the ventral hippocampus for hyperexcitability.

Finally, an interesting observation, possibly relevant to our discussion, has been made by Derchansky *et al*. (134) who found that the epileptiform activity induced in the acutely-isolated whole hippocampus *in vitro* is increased in the ventral hippocampus after a transverse cut that separated the ventral from the dorsal segment of the structure. This observation allows us to hypothesize that longitudinal connections in the dorsoventral direction may play a role in regulating the excitability in the ventral hippocampus. Perhaps relevant to this issue is the observation that epileptiform discharges initiated in the dorsal hippocampus propagate toward the ventral hippocampus very slowly (27).

7.3. Synaptic computations

The activity-dependent changes in short-lasting synaptic effectiveness are widely observed phenomena that appear therefore to be of fundamental importance in neural information processing (262, 332–336) including memory processing (337) and synaptic filtering of information (338–341). Phenomena of short-term plasticity including synaptic facilitation may play important roles in the synaptic filtering of incoming information that is contained in the firing pattern of presynaptic cells (335, 341, 342). Accordingly, short-term plasticity conveys frequency-filtering properties to synapses (343–345). As discussed in the section 5.3. the CA1 synapses in the dorsal and the ventral hippocampus display striking differences in several forms of short-term plasticity (179, 186, 187, 193). Thus, dorsal synapses show robust paired-pulse facilitation and both frequency facilitation (between 1 and 40 Hz) and frequency depression (at frequencies above 40 Hz). On the contrary, the ventral synapses show reduced paired-pulse facilitation and frequency depression (186, 187). Accordingly, the synapses of the dorsal and ventral hippocampus show characteristics of band-pass and low-pass filters respectively (335, 340). Depressing synapses dramatically increase the sensitivity of a neuron to small changes in the input firing rate (335, 345). This may be especially relevant for the spontaneous generation of memory-related activity of SPW-Rs in the recurrent CA3 network of the ventral hippocampus. Interestingly, subtle increase in neuronal excitability in the ventral CA3 hippocampal field through synaptic actions of the endogenously released stress-related neuropeptide corticotrophin-releasing hormone promotes the generation of SPW-Rs (346).

The synaptic facilitation is inversely related to the initial probability of transmitter release (213) and it has therefore been suggested that the probability of transmitter release is lower in the dorsal than in ventral hippocampus (186, 187) although some evidence does not support this suggestion (193). Low probability synapses are unreliable synapses that display high degree of short-term plasticity and they can become particularly reliable when the presynaptic activity is organized in short bursts of action potentials (343), which is the typical mode of activity of hippocampal pyramidal cells (317). Indeed, dorsal but not ventral hippocampal synapses show a remarkable facilitation when stimulated by short-bursts of presynaptic pulses (179). The burst represent a very reliable mode of presynaptic activity that can trigger postsynaptic firing by minimizing the number of active inputs required to trigger an action potential and they also play an important role in synaptic plasticity (343). Indeed, short-bursts produce strong enhancement in postsynaptic firing in the dorsal but not the ventral hippocampus and this appears to have a decisive influence on reducing the threshold for induction of LTP in dorsal as compared with ventral synapses (179).

Therefore, based on above discussion and taking also into account the postulate that “short-term changes in synaptic efficacy due to transient changes in the reliability of transmitter release can provide a mechanism for the generation of potentially infinite diversity of synaptic inputs” (347) it is proposed that the dorsoventral differences in short-term plasticity may have very important implications for the synaptic

information processing in the dorsal and the ventral hippocampus. Interestingly, the response of the synaptic circuitry of the dorsal but not the ventral hippocampus is selectively enhanced at an input frequency of 5 Hz. Thus, the postsynaptic responses, which involve a substantial NMDAR-mediated component and are evoked by paired-pulse stimulation or burst stimulation or a train of consecutive pulses at 5 Hz are strongly facilitated in the dorsal but not the ventral hippocampus (179, 186, 193). In addition, the frequency of occurrence of SPW-Rs in clusters is also around 5 Hz (30). Thus, these dorsoventral differences in the responsiveness of the intrinsic circuitry to theta frequency inputs may to some extent underlie the prominence of the theta oscillation along the ventral-dorsal axis of the hippocampus (28, 31). These associations of the dorsal hippocampus with the theta frequency is consistent with the selective involvement of the dorsal hippocampus to spatial coding (23) to which the theta oscillation appear to play an important role (9).

7.4. Implications for pathology

Practically, the temporal lobe epilepsy in human typically involves the anterior hippocampus. Similarly, the ventral hippocampus in rodents, which have been widely used in basic epilepsy research, is the most susceptible part of the hippocampus to epileptiform discharges. However, despite the well established higher susceptibility of the ventral (or anterior) part of the hippocampus to epileptic/epileptiform activity and the existence of various putative factors the precise underlying mechanisms are not yet clear. A potential factor for this unknowing may be the fact that epileptic activity in most *in vivo* studies was recorded from the dorsal hippocampus. Similarly, in the vast majority of the *in vitro* studies, which have mainly been performed in hippocampal slices, the exact location of the hippocampus from which the slices were prepared was neglected. As described above several mechanisms that appear to underlie the increased excitability of the ventral hippocampus, including intrinsic cell properties and GABAergic inhibition, may also contribute to drive this part of the hippocampus into hyperexcitability resulting thus in the generation of epileptiform activities. Indeed, commonly used antiepileptic medications work to increase the actions of GABA or to reduce neuronal excitability. However, mechanisms that influence network excitability in a less direct way may be particularly suitable in the treatment of epilepsy. Among these mechanisms, the recently studied system of endocannabinoids appears to be especially promising (348, 349). Endocannabinoids control hyperexcitability (350, 351) and activation of endocannabinoid CB1 receptors limits epileptic seizures in animals (352–354) and alleviate epileptiform discharges *in vitro* (355, 356). Although CB1 receptors control the excitatory and the inhibitory synaptic transmission (357, 358), in the hippocampus activation of CB1 reduces mainly the excitatory transmission (221, 354). Therefore, considering the recently shown absent tonic activity of CB1 receptors in the ventral hippocampus under intense neuronal activity (188) research on CB1 receptors specifically in the ventral hippocampus may provide encouraging results for new treatment of temporal lobe epilepsy.

8. CONCLUSIONS & FUTURE DIRECTIONS

A considerable amount of electrophysiological studies performed mainly during the past two decades strongly provides compelling evidence for the existence of important diversification in the fine organization of the intrinsic neural circuitry along the long axis of the hippocampus. Most of these observations converge to the idea that an emergent property that diversifies the local circuitries in the dorsal and the ventral hippocampus is the network excitability, which appears to be higher in the ventral hippocampus. Under conditions that favor increased excitability the ventral hippocampus slips into a state of hyperexcitability observed as a higher propensity to epileptiform activity. However, under normal conditions the higher intrinsic excitability of the ventral hippocampus is virtually balanced by a number of compensatory mechanisms. Importantly, the higher intrinsic excitability of the ventral hippocampus appears to be an essential property that can support the initiation of the basic network oscillation of SPW-Rs in this segment of the hippocampus; then SPW-Rs can propagate toward the dorsal hippocampus. The theta oscillation, on the other hand, may follow a dorsal-ventral direction of propagation. These conclusions are schematically summarized in Figure 1. Differences in synaptic transmission and synaptic plasticity between the dorsal and the ventral hippocampus may endow the two hippocampal segments with distinct computational properties and capabilities that conform to their specific functional roles.

It is clear that most of the questions regarding the diversification of the intrinsic neuronal circuitries of the dorsal and ventral hippocampus are open. Some major questions may are the following: How the synapses of the dorsal and the ventral hippocampus respond to physiologically relevant frequencies of activation? Which are the mechanisms underlying the dorsoventral differences in short-term and long-term synaptic plasticity? How the various neuromodulators systems, which appear to quantitatively differ along the long axis of the hippocampus, regulate synaptic transmission, synaptic plasticity and neuronal excitability and how this regulation is translated into the functioning of the local neural circuitry? What roles are played by the three different subfields, DG, CA3 and CA1 in the dorsal and the ventral hippocampus?

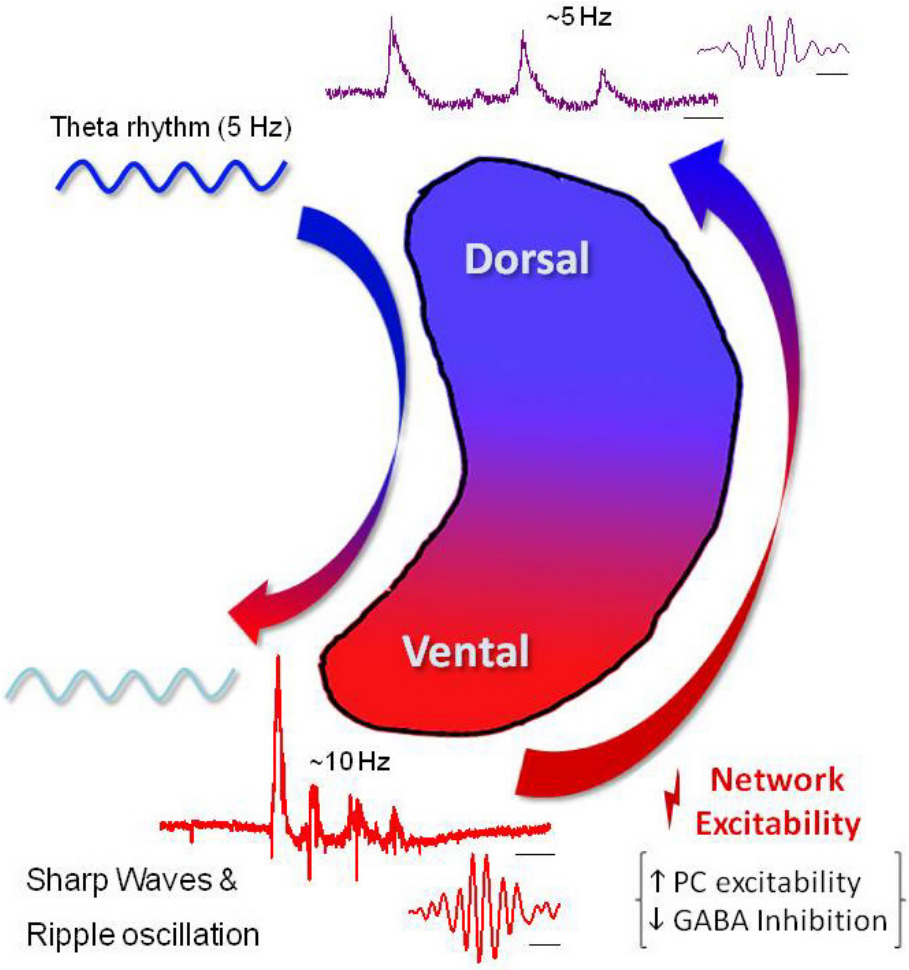

Figure 1. Schematic diagram summarizing some of the conclusions drawn from the present survey and illustrating that sharp wave-ripples (SPW-Rs) and theta rhythm may preferentially propagate along a ventral-dorsal and dorsal-ventral direction respectively. Note that SPW-Rs inside clusters occur at a frequency of ~10 Hz and ~5 Hz in the ventral and the dorsal hippocampus respectively. Calibration: 100 ms and 10 ms in sharp wave and ripple oscillation traces respectively. An important local network property that can support the initiation of SPW-Rs in the ventral hippocampus is the increased excitability in this part of the hippocampus. The increased pyramidal cell (PC) intrinsic excitability and the reduced GABAergic inhibition are considered among the most important mechanisms contributing to the increased network excitability in the ventral hippocampus.

Whether and how the physiological rhythms of the hippocampus are affected in neurological disorders known to involve hippocampus, such as Alzheimer disease, depression, schizophrenia and autism? Which physiological properties of the neuronal circuit change gradually and which display abrupt changes along the hippocampal long axis? Ultimately, how the plethora of intrinsic circuitry specializations determine the information processing through the hippocampus and how the specialized signal processing by the different segments of the hippocampus support their distinct involvement to various hippocampal-dependent behaviors?

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10. REFERENCES

1. M. P. Witter and D. G. Amaral: Hippocampal Formation. In: *The Rat Nervous System*. Ed G. Paxinos. Academic Press, San Diego (2004)
DOI: 10.1016/B978-012547638-6/50022-5

2. H. M. Duvernoy: The human hippocampus: functional anatomy, vascularization and serial sections with MRI. Springer Science & Business Media, (2005)

3. H. Eichenbaum: Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron*, 44(1), 109–20 (2004)
DOI: 10.1016/j.neuron.2004.08.028

4. R. G. Morris: Theories of Hippocampal Function. In: *The Hippocampus Book*. Ed P. Andersen, Morris, R., Amaral, D., Bliss, T., O'Keefe, J. Oxford University Oress, Oxford (2007)

5. L. R. Squire: Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev*, 99(2), 195–231 (1992)
DOI: 10.1037/0033-295X.99.2.195

6. J. O'Keefe and L. Nadel: The hippocampus as a cognitive map. Clarendon Press, Oxford (1978)

7. J. O'Keefe, N. Burgess, J. G. Donnett, K. J. Jeffery and E. A. Maguire: Place cells, navigational accuracy, and the human hippocampus. *Philos Trans R Soc Lond B Biol Sci*, 353(1373), 1333–40 (1998)

8. E. A. Maguire, N. Burgess, J. G. Donnett, R. S. Frackowiak, C. D. Frith and J. O'Keefe: Knowing where and getting there: a human navigation network. *Science*, 280(5365), 921–4 (1998)
DOI: 10.1126/science.280.5365.921

9. G. Buzsaki and E. I. Moser: Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat Neurosci*, 16(2), 130–8 (2013)

10. D. M. Bannerman, R. Sprengel, D. J. Sanderson, S. B. McHugh, J. N. Rawlins, H. Monyer and P. H. Seeburg: Hippocampal synaptic plasticity, spatial memory and anxiety. *Nat Rev Neurosci*, 15(3), 181–192 (2014)
DOI: 10.1038/nrn3677

11. J. J. Kim and M. S. Fanselow: Modality-specific retrograde amnesia of fear. *Science*, 256(5057), 675–7 (1992)
DOI: 10.1126/science.1585183

12. K. A. Goosens: Hippocampal regulation of aversive memories. *Curr Opin Neurobiol*, 21(3), 460–6 (2011)

13. E. Engin and D. Treit: The role of hippocampus in anxiety: intracerebral infusion studies. *Behav Pharmacol*, 18(5–6), 365–74 (2007)

14. T. Bast and J. Feldon: Hippocampal modulation of sensorimotor processes. *Prog Neurobiol*, 70(4), 319–45 (2003)
DOI: 10.1016/S0301-0082(03)00112-6

15. B. H. Bland and S. D. Oddie: Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. *Behav Brain Res*, 127(1–2), 119–36 (2001)
DOI: 10.1016/S0166-4328(01)00358-8

16. K. R. Hughes: Dorsal and ventral hippocampus lesions and maze learning: influence of preoperative environment. *Can J Psychol*, 19(4), 325–32 (1965)
DOI: 10.1037/h0082915

17. A. Siegel and J. P. Flynn: Differential effects of electrical stimulation and lesions of the hippocampus and adjacent regions upon attack behavior in cats. *Brain Res*, 7(2), 252–67 (1968)
DOI: 10.1016/0006-8993(68)90102-9

18. L. D. Grant and L. E. Jarrard: Functional dissociation within hippocampus. *Brain Research*, 10(3), 392–401 (1968)
DOI: 10.1016/0006-8993(68)90207-2

19. W. R. Adey: Recent studies of the rhinencephalon in relation to temporal lobe epilepsy and behavior disorders. *Int Rev Neurobiol*, 1, 1–46 (1959)
DOI: 10.1016/S0074-7742(08)60313-X

20. W. B. Scoville and B. Milner: Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry*, 20(1), 11–21 (1957)
DOI: 10.1136/jnnp.20.1.11

21. M. B. Moser and E. I. Moser: Functional differentiation in the hippocampus. *Hippocampus*, 8(6), 608–19 (1998)

22. M. S. Fanselow and H. W. Dong: Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, 65(1), 7–19 (2010)

23. B. A. Strange, M. P. Witter, E. S. Lein and E. I. Moser: Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci*, 15(10), 655–69 (2014)

24. P. Y. Risold and L. W. Swanson: Structural evidence for functional domains in the rat hippocampus. *Science*, 272(5267), 1484–6 (1996)
DOI: 10.1126/science.272.5267.1484

25. M. P. Witter, F. G. Wouterlood, P. A. Naber and T. Van Haeften: Anatomical organization of the parahippocampal-hippocampal network. *Ann N Y Acad Sci*, 911, 1–24 (2000)
DOI: 10.1111/j.1749-6632.2000.tb06716.x

26. W. T. Niemer, E. W. Powell and E. F. Goodfellow: The subcortex and hypothalamic after-discharge in the cat. *Electroencephalogr Clin Neurophysiol*, 12, 345–58 (1960)
DOI: 10.1016/0013-4694(60)90009-2

27. R. Elul: Regional Differences in the Hippocampus of the Cat. I. Specific Discharge Patterns of the Dorsal and Ventral Hippocampus and Their Role in Generalized Seizures. *Electroencephalogr Clin Neurophysiol*, 16, 470–88 (1964)
DOI: 10.1016/0013-4694(64)90089-6

28. L. L. Long, J. G. Bunce and J. J. Chrobak: Theta variation and spatiotemporal scaling along the septotemporal axis of the hippocampus. *Front Syst Neurosci*, 9, 37 (2015)

29. J. Patel, E. W. Schomburg, A. Berenyi, S. Fujisawa and G. Buzsaki: Local generation and propagation of ripples along the septotemporal axis of the hippocampus. *J Neurosci*, 33(43), 17029–41 (2013)

30. S. Kouvaros and C. Papatheodoropoulos: Prominent differences in sharp wave – ripples and complex spike bursts between the dorsal and the ventral rat hippocampus. *Neuroscience* (2017)

31. R. Goutagny, J. Jackson and S. Williams: Self-generated theta oscillations in the hippocampus. *Nat Neurosci*, 12(12), 1491–3 (2009)

32. R. G. Nilges: The arteries of the mammalian cornu ammonis. *The Journal of Comparative Neurology*, 80(2), 177–190 (1944)

33. I. Grivas, H. Michaloudi, C. Batzios, M. Chiotelli, C. Papatheodoropoulos, G. Kostopoulos and G. C. Papadopoulos: Vascular network of the rat hippocampus is not homogeneous along the septotemporal axis. *Brain Res*, 971(2), 245–9 (2003)
DOI: 10.1016/S0006-8993(03)02475-2

34. C. W. Dunlop: Effects of carbon dioxide on deep structures of temporal lobe of the brain in the marsupial phalanger. *Am J Physiol*, 190(1), 172–6 (1957)

35. R. N. Auer, M. L. Jensen and I. Q. Whishaw: Neurobehavioral deficit due to ischemic brain damage limited to half of the CA1 sector of the hippocampus. *J Neurosci*, 9(5), 1641–7 (1989)

36. D. Ashton, J. Van Reempts, M. Haseldonckx and R. Willems: Dorsal-ventral gradient in vulnerability of CA1 hippocampus to ischemia: a combined histological and electrophysiological study. *Brain Res*, 487(2), 368–72 (1989)
DOI: 10.1016/0006-8993(89)90842-1

37. A. Rami, F. Ausmeir, J. Winckler and J. Krieglstein: Differential effects of scopolamine on neuronal survival in ischemia and glutamate neurotoxicity: relationships to the excessive vulnerability of the dorsoseptal hippocampus. *J Chem Neuroanat*, 13(3), 201–8 (1997)
DOI: 10.1016/S0891-0618(97)00044-6

38. W. J. Nauta: An experimental study of the fornix system in the rat. *J Comp Neurol*, 104(2), 247–71 (1956)
DOI: 10.1002/cne.901040205

39. E. W. Powell, J. Haggart, E. Good-Fellow and W. T. Niemer: Hypothalamic seizures from stimulation of rhinencephalon and isocortex in cat. *Neurology*, 7(10), 689–96 (1957)
DOI: 10.1212/WNL.7.10.689

40. W. R. Adey, S. Sunderland and C. W. Dunlop: The entorhinal area; electrophysiological studies of its interrelations with rhinencephalic structures and the brainstem. *Electroencephalogr Clin Neurophysiol*, 9(2), 309–24 (1957)
DOI: 10.1016/0013-4694(57)90064-0

41. E. F. Goodfellow and W. T. Niemer: The spread of after-discharge from stimulation of the rhinencephalon in the cat. *Electroencephalography and Clinical Neurophysiology*, 13(5), 710–721 (1961)
DOI: 10.1016/0013-4694(61)90103-1

42. R. Elul: Regional Differences in the Hippocampus of the Cat. Ii. Projections of the Dorsal and Ventral Hippocampus. *Electroencephalogr Clin Neurophysiol*, 16, 489–502 (1964)
DOI: 10.1016/0013-4694(64)90090-2

43. O. Andy and J. Mukawa: Amygdaloid and hippocampal after-discharges propagated to septum. In: *Electroencephalography and Clinical Neurophysiology.* Elsevier Sci Ireland Ltd Customer Relations Manager, bay 15, Shannon Industrial Estate Co, Clare, Ireland., (1961)

44. M. Monnier and D. Gangloff: Les fonctions integratives du rhinencephale. In: *Physiologie et pathologie du rhinencephale.* Ed T. Alajouanine. Masson & Cie., Paris (1961)

45. P. D. MacLean: The limbic system with respect to self-preservation and the preservation of the species. *The Journal of nervous and mental disease*, 127(1), 1–11 (1958)
DOI: 10.1097/00005053-195807000-00001

46. W. R. Adey, C. W. Dunlop and C. E. Hendrix: Hippocampal slow waves. Distribution and phase relationships in the course of approach learning. *Arch Neurol*, 3, 74–90 (1960)
DOI:10.1001/archneur.1960.00450010074007

47. W. R. Adey and D. O. Walter: Application of phase detection and averaging techniques in computer analysis of EEG records in the cat. *Exp Neurol*, 7, 186–209 (1963)
DOI: 10.1016/0014-4886(63)90054-2

48. P. A. Fried: Limbic system lesions in rats: differential effects in an approach-avoidance task. *J Comp Physiol Psychol*, 74(3), 349–53 (1971)
DOI: 10.1037/h0030560

49. L. Nadel: Dorsal and ventral hippocampal lesions and behavior. *Physiology & Behavior*, 3(6), 891–900 (1968)
DOI: 10.1016/0031-9384(68)90174-1

50. M. A. Brazier: Regional activities within the human hippocampus and hippocampal gyrus. *Exp Neurol*, 26(2), 254–68 (1970)
DOI: 10.1016/0014-4886(70)90132-9

51. D. Purpura: Discussion. In: *The central nervous system and behavior.* Ed M. A. Brazier. Josiah Macy Jr. Foundation, New York (1959)

52. A. C. Bragdon, D. M. Taylor and W. A. Wilson: Potassium-induced epileptiform activity in area CA3 varies markedly along the septotemporal axis of the rat hippocampus. *Brain Res*, 378(1), 169–73 (1986)
DOI: 10.1016/0006-8993(86)90300-8

53. H. M. Sinnamon, S. Freniere and J. Kootz: Rat hippocampus and memory for places of changing significance. *J Comp Physiol Psychol*, 92(1), 142–55 (1978)
DOI: 10.1037/h0077446

54. R. Stevens and A. Cowey: Effects of dorsal and ventral hippocampal lesions on spontaneous alternation, learned alternation and probability learning in rats. *Brain Res*, 52, 203–24 (1973)
DOI: 10.1016/0006-8993(73)90659-8

55. E. Moser, M. B. Moser and P. Andersen: Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *J Neurosci*, 13(9), 3916–25 (1993)

56. M. B. Moser, E. I. Moser, E. Forrest, P. Andersen and R. G. Morris: Spatial learning with a minislab in the dorsal hippocampus. *Proc Natl Acad Sci U S A*, 92(21), 9697–701 (1995)
DOI: 10.1073/pnas.92.21.9697

57. M. Colombo, T. Fernandez, K. Nakamura and C. G. Gross: Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. *J Neurophysiol*, 80(2), 1002–5 (1998)

58. B. J. Hock, Jr. and M. D. Bunsey: Differential effects of dorsal and ventral hippocampal lesions. *J Neurosci*, 18(17), 7027–32 (1998)

59. A. Siegel and J. P. Tassoni: Differential efferent projections from the ventral and dorsal hippocampus of the cat. *Brain Behav Evol*, 4(3), 185–200 (1971)
DOI: 10.1159/000125433

60. L. W. Swanson and W. M. Cowan: An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J Comp Neurol*, 172(1), 49–84 (1977)

61. N. M. van Strien, N. L. Cappaert and M. P. Witter: The anatomy of memory: an interactive overview of the parahippocampal-

hippocampal network. *Nat Rev Neurosci*, 10(4), 272–82 (2009)

62. M. P. Witter, H. J. Groenewegen, F. H. Lopes da Silva and A. H. Lohman: Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. *Prog Neurobiol*, 33(3), 161–253 (1989) DOI: 10.1016/0301-0082(89)90009-9

63. G. D. Petrovich, N. S. Canteras and L. W. Swanson: Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. *Brain Res Brain Res Rev*, 38(1–2), 247–89 (2001) DOI: 10.1016/S0165-0173(01)00080-7

64. M. Pikkarainen, S. Ronkko, V. Savander, R. Insausti and A. Pitkanen: Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. *J Comp Neurol*, 403(2), 229–60 (1999) DOI:10.1002/(SICI)1096-9861(19990111)403:2<229::AID-CNE7>3.0.CO;2-P

65. T. Van Groen and F. H. Lopes da Silva: Septotemporal distribution of entorhinal projections to the hippocampus in the cat: electrophysiological evidence. *J Comp Neurol*, 238(1), 1–9 (1985)

66. P. H. Lee, C. W. Xie, D. V. Lewis, W. A. Wilson, C. L. Mitchell and J. S. Hong: Opioid-induced epileptiform bursting in hippocampal slices: higher susceptibility in ventral than dorsal hippocampus. *J Pharmacol Exp Ther*, 253(2), 545–51 (1990)

67. P. Andersen, T. V. Bliss and K. K. Skrede: Lamellar organization of hippocampal pathways. *Exp Brain Res*, 13(2), 222–38 (1971) DOI: 10.1007/BF00234087

68. P. Andersen, T. V. Bliss, T. Lomo, L. I. Olsen and K. K. Skrede: Lamellar organization of hippocampal excitatory pathways. *Acta Physiol Scand*, 76(1), 4A-5A (1969)

69. P. Andersen, A. F. Soleng and M. Raastad: The hippocampal lamella hypothesis revisited. *Brain Res*, 886(1–2), 165–171 (2000) DOI: 10.1016/S0006-8993(00)02991-7

70. R. Lorente de No: Studies on the structure of the cerebral cortex. II. . *J Psychol Neurol (Lpz)*, 46, 113–177 (1934)

71. H. McIlwain, G. Anguiano and J. D. Cheshire: Electrical stimulation *in vitro* of the metabolism of glucose by mammalian cerebral cortex. *Biochem J*, 50(1), 12–8 (1951) DOI: 10.1042/bj0500012

72. C. Yamamoto and H. McIlwain: Electrical activities in thin sections from the mammalian brain maintained in chemically-defined media *in vitro*. *J Neurochem*, 13(12), 1333–43 (1966) DOI: 10.1111/j.1471-4159.1966.tb04296.x

73. R. Dingledine, J. Dodd and J. S. Kelly: The *in vitro* brain slice as a useful neurophysiological preparation for intracellular recording. *J Neurosci Methods*, 2(4), 323–62 (1980) DOI: 10.1016/0165-0270(80)90002-3

74. G. L. Collingridge: The brain slice preparation: a tribute to the pioneer Henry McIlwain. *J Neurosci Methods*, 59(1), 5–9 (1995) DOI: 10.1016/0165-0270(94)00187-L

75. T. J. Teyler: Use of brain slices to study long-term potentiation and depression as examples of synaptic plasticity. *Methods*, 18(2), 109–116 (1999) DOI: 10.1006/meth.1999.0764

76. D. G. Amaral and M. P. Witter: The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience*, 31(3), 571–91 (1989) DOI: 10.1016/0306-4522(89)90424-7

77. R. S. Sloviter and T. Lomo: Updating the lamellar hypothesis of hippocampal organization. *Front Neural Circuits*, 6, 102 (2012)

78. G. Tushev and E. M. Schuman: Rethinking Functional Segregation: Gradients of Gene Expression in Area CA1. *Neuron*, 89(2), 242–3 (2016)

79. M. S. Cembrowski, J. L. Bachman, L. Wang, K. Sugino, B. C. Shields and N. Spruston: Spatial Gene-Expression Gradients Underlie Prominent Heterogeneity of CA1 Pyramidal Neurons. *Neuron*, 89(2), 351–68 (2016)

80. J. O'Keefe: Hippocampal neurophysiology in the behaving animal. In: *The hippocampus book.* Ed P. Andersen, R. Morris, D. Amaral,

T. Bliss&J. O'Keefe. Oxford University Press, Oxford (2007)

81. G. Buzsaki: Rhythms of the brain. Oxford University Press, Oxford (2006) DOI: 10.1093/acprof:oso/9780195301069.001.0001

82. L. L. Colgin: Rhythms of the hippocampal network. *Nat Rev Neurosci*, 17(4), 239–49 (2016)

83. L. L. Colgin: Mechanisms and functions of theta rhythms. *Annu Rev Neurosci*, 36, 295–312 (2013) DOI: 10.1146/annurev-neuro-062012-170330

84. W. Ramadan, O. Eschenko and S. J. Sara: Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. *PLoS One*, 4(8), e6697 (2009) DOI: 10.1371/journal.pone.0006697

85. A. C. Singer and L. M. Frank: Rewarded outcomes enhance reactivation of experience in the hippocampus. *Neuron*, 64(6), 910–21 (2009)

86. S. P. Jadhav, C. Kemere, P. W. German and L. M. Frank: Awake hippocampal sharp-wave ripples support spatial memory. *Science*, 336(6087), 1454–8 (2012)

87. G. Girardeau, K. Benchenane, S. I. Wiener, G. Buzsaki and M. B. Zugaro: Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.*, 12(10), 1222–3 (2009)

88. G. Buzsáki: Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25(10), 1073–1188 (2015)

89. T. J. Davidson, F. Kloosterman and M. A. Wilson: Hippocampal replay of extended experience. *Neuron*, 63(4), 497–507 (2009)

90. A. S. Gupta, M. A. van der Meer, D. S. Touretzky and A. D. Redish: Hippocampal replay is not a simple function of experience. *Neuron*, 65(5), 695–705 (2010)

91. G. Dragoi and S. Tonegawa: Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature*, 469(7330), 397–401 (2011)

92. J. Y. Yu and L. M. Frank: Hippocampal-cortical interaction in decision making. *Neurobiol Learn Mem*, 117, 34–41 (2015) DOI: 10.1016/j.nlm.2014.02.002

93. L. L. Colgin and E. I. Moser: Gamma oscillations in the hippocampus. *Physiology (Bethesda)*, 25(5), 319–29 (2010)

94. P. D. MacLean: The limbic system with respect to two basic life principles. *The central nervous system and behavior*, 31–118 (1959)

95. M. Jouvet: Neurophysiology of the states of sleep. *Physiol Rev*, 47(2), 117–77 (1967)

96. E. V. Lubenov and A. G. Siapas: Hippocampal theta oscillations are travelling waves. *Nature*, 459(7246), 534–9 (2009)

97. S. Royer, A. Sirota, J. Patel and G. Buzsaki: Distinct representations and theta dynamics in dorsal and ventral hippocampus. *J Neurosci*, 30(5), 1777–87 (2010)

98. J. R. Hinman, S. C. Penley, L. L. Long, M. A. Escabi and J. J. Chrobak: Septotemporal variation in dynamics of theta: speed and habituation. *J Neurophysiol*, 105(6), 2675–86 (2011)

99. C. H. Vanderwolf: Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr Clin Neurophysiol*, 26(4), 407–418 (1969) DOI: 10.1016/0013-4694(69)90092-3

100. G. Buzsaki, L. W. Leung and C. H. Vanderwolf: Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.*, 287(2), 139–71 (1983) DOI: 10.1016/0165-0173(83)90037-1

101. G. Buzsaki, J. Czopf, I. Kondakor, A. Bjorklund and F. H. Gage: Cellular activity of intracerebrally transplanted fetal hippocampus during behavior. *Neuroscience*, 22(3), 871–83 (1987) DOI: 10.1016/0306-4522(87)92966-6

102. S. S. Suzuki and G. K. Smith: Spontaneous EEG spikes in the normal hippocampus. IV. Effects of medial septum and entorhinal cortex lesions. *Electroencephalogr Clin Neurophysiol*, 70(1), 73–83 (1988) DOI: 10.1016/0013-4694(88)90197-6

103. C. Papatheodoropoulos: Patterned activation of hippocampal network (approximately 10 Hz) during *in vitro* sharp wave-ripples. *Neuroscience*, 168(2), 429–42 (2010)

104. C. Papatheodoropoulos and G. Kostopoulos: Spontaneous, low frequency (approximately 2–3 Hz) field activity generated in rat ventral hippocampal slices perfused with normal medium. *Brain Res Bull*, 57(2), 187–93 (2002)

105. N. Maier, V. Nimmrich and A. Draguhn: Cellular and network mechanisms underlying spontaneous sharp wave-ripple complexes in mouse hippocampal slices. *J Physiol*, 550(Pt 3), 873–87 (2003)
DOI: 10.1113/jphysiol.2003.044602

106. L. L. Colgin, D. Kubota, Y. Jia, C. S. Rex and G. Lynch: Long-term potentiation is impaired in rat hippocampal slices that produce spontaneous sharp waves. *J Physiol*, 558(Pt 3), 953–61 (2004)

107. D. Kubota, L. L. Colgin, M. Casale, F. A. Brucher and G. Lynch: Endogenous waves in hippocampal slices. *J Neurophysiol*, 89(1), 81–89 (2003)
DOI: 10.1152/jn.00542.2002

108. C. Wu, H. Shen, W. P. Luk and L. Zhang: A fundamental oscillatory state of isolated rodent hippocampus. *J Physiol*, 540(Pt 2), 509–527 (2002)
DOI: 10.1113/jphysiol.2001.013441

109. P. Aivar, M. Valero, E. Bellistri and L. M. de la Prida: Extracellular calcium controls the expression of two different forms of ripple-like hippocampal oscillations. *Journal of Neuroscience*, 34(8), 2989–3004 (2014)

110. M. Mizunuma, H. Norimoto, K. Tao, T. Egawa, K. Hanaoka, T. Sakaguchi, H. Hioki, T. Kaneko, S. Yamaguchi, T. Nagano, N. Matsuki and Y. Ikegaya: Unbalanced excitability underlies offline reactivation of behaviorally activated neurons. *Nat Neurosci*, 17(4), 503–5 (2014)

111. M. F. Carr, S. P. Jadhav and L. M. Frank: Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat Neurosci*, 14(2), 147–53 (2011)

112. G. Buzsaki: Hippocampal sharp waves: their origin and significance. *Brain Res*, 398(2), 242–252 (1986)
DOI: 10.1016/0006-8993(86)91483-6

113. F. K. Skinner, C. Wu and L. Zhang: Phase-coupled oscillator models can predict hippocampal inhibitory synaptic connections. *Eur J Neurosci*, 13(12), 2183–94 (2001)
DOI: 10.1046/j.0953-816x.2001.01594.x

114. J. H. Sadowski, M. W. Jones and J. R. Mellor: Sharp-Wave Ripples Orchestrate the Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus. *Cell Rep*, 14(8), 1916–29 (2016)

115. G. Q. Bi and M. M. Poo: Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J Neurosci*, 18(24), 10464–72 (1998)

116. C. Papatheodoropoulos, E. Sotiriou, D. Kotzadimitriou and P. Drimala: At clinically relevant concentrations the anaesthetic/amnesic thiopental but not the anticonvulsant phenobarbital interferes with hippocampal sharp wave-ripple complexes. *BMC Neurosci*, 8, 60 (2007)

117. C. Papatheodoropoulos and E. Koniaris: alpha5GABAA receptors regulate hippocampal sharp wave-ripple activity *in vitro*. *Neuropharmacology*, 60(4), 662–73 (2011)

118. P. Byrne, S. Becker and N. Burgess: Remembering the past and imagining the future: a neural model of spatial memory and imagery. *Psychol Rev*, 114(2), 340–75 (2007)

119. C. M. Atance and D. K. O'Neill: Episodic future thinking. *Trends Cogn Sci*, 5(12), 533–539 (2001)
DOI: 10.1016/S1364-6613(00)01804-0

120. A. D'Argembeau, O. Jeunehomme, S. Majerus, C. Bastin and E. Salmon: The neural basis of temporal order processing in past and future thought. *J Cogn Neurosci*, 27(1), 185–97 (2015)

121. D. L. Schacter, D. R. Addis, D. Hassabis, V. C. Martin, R. N. Spreng and K. K. Szpunar:

The future of memory: remembering, imagining, and the brain. *Neuron*, 76(4), 677–94 (2012)

122. R. Jung: Hirnelektrische Untersuchungen über den Elektrokrampf: Die Erregungsabläufe in corticalen und subcorticalen Hirnregionen bei Katze und Hund. *Archiv für Psychiatrie und Nervenkrankheiten*, 183(1), 206–244 (1949)

123. W. T. Liberson and K. Akert: Hippocampal seizure states in guinea pig. *Electroencephalogr Clin Neurophysiol*, 7(2), 211–22 (1955)
DOI: 10.1016/0013-4694(55)90036-5

124. J. D. Green and T. Shimamoto: Hippocampal seizures and their propagation. *AMA Arch Neurol Psychiatry*, 70(6), 687–702 (1953)
DOI: 10.1001/archneurpsyc.1953.02320360002001

125. J. D. Green: THE HIPPOCAMPUS. *Physiol Rev*, 44, 561–608 (1964)

126. O. J. Andy and K. Akert: Seizure patterns induced by electrical stimulation of hippocampal formation in the cat. *J Neuropathol Exp Neurol*, 14(2), 198–213 (1955)
DOI: 10.1097/00005072-195504000-00004

127. B. E. Alger: Hippocampus: Electrophysiological studies of epileptiform activity *in vitro*. In: *Brain Slices*. Springer, (1984)
DOI: 10.1007/978-1-4684-4583-1_7

128. P. A. Schwartzkroin: Role of the hippocampus in epilepsy. *Hippocampus*, 4(3), 239–42 (1994)

129. A. Chatzikonstantinou: Epilepsy and the hippocampus. *Front Neurol Neurosci*, 34, 121–42 (2014)
DOI: 10.1159/000356435

130. D. D. Spencer, S. S. Spencer, R. H. Mattson, P. D. Williamson and R. A. Novelly: Access to the posterior medial temporal lobe structures in the surgical treatment of temporal lobe epilepsy. *Neurosurgery*, 15(5), 667–71 (1984)
DOI: 10.1227/00006123-198411000-00005

131. T. L. Babb, W. J. Brown, J. Pretorius, C. Davenport, J. P. Lieb and P. H. Crandall: Temporal lobe volumetric cell densities in temporal lobe epilepsy. *Epilepsia*, 25(6), 729–40 (1984)
DOI: 10.1111/j.1528-1157.1984.tb03484.x

132. M. Quigg, E. H. Bertram and T. Jackson: Longitudinal distribution of hippocampal atrophy in mesial temporal lobe epilepsy. *Epilepsy Res*, 27(2), 101–10 (1997)
DOI: 10.1016/S0920-1211(97)01026-7

133. R. D. Traub, J. G. Jefferys and R. Miles: Analysis of the propagation of disinhibition-induced after-discharges along the guinea-pig hippocampal slice *in vitro*. *J Physiol*, 472, 267–87 (1993)
DOI: 10.1113/jphysiol.1993.sp019946

134. M. Derchansky, E. Shahar, R. A. Wennberg, M. Samoilova, S. S. Jahromi, P. A. Abdelmalik, L. Zhang and P. L. Carlen: Model of frequent, recurrent, and spontaneous seizures in the intact mouse hippocampus. *Hippocampus*, 14(8), 935–947 (2004)
DOI: 10.1002/hipo.20007

135. M. Derchansky, D. Rokni, J. T. Rick, R. Wennberg, B. L. Bardakjian, L. Zhang, Y. Yarom and P. L. Carlen: Bidirectional multisite seizure propagation in the intact isolated hippocampus: the multifocality of the seizure “focus”. *Neurobiol Dis*, 23(2), 312–28 (2006)

136. V. Dzhala, I. Khalilov, Y. Ben-Ari and R. Khazipov: Neuronal mechanisms of the anoxia-induced network oscillations in the rat hippocampus *in vitro*. *J Physiol*, 536 (Pt 2), 521–31 (2001)
DOI: 10.1111/j.1469-7793.2001.0521c.xd

137. H. J. Luhmann, V. I. Dzhala and Y. Ben-Ari: Generation and propagation of 4-AP-induced epileptiform activity in neonatal intact limbic structures *in vitro*. *Eur J Neurosci*, 12(8), 2757–68 (2000)
DOI: 10.1046/j.1460-9568.2000.00156.x

138. M. Gilbert, R. J. Racine and G. K. Smith: Epileptiform burst responses in ventral vs dorsal hippocampal slices. *Brain Res*, 361(1–2), 389–91 (1985)
DOI: 10.1016/0006-8993(85)91309-5

139. C. Borck and J. G. Jefferys: Seizure-like events in disinhibited ventral slices of adult rat hippocampus. *J Neurophysiol*, 82(5), 2130–42 (1999)

140. C. Papatheodoropoulos, C. Moschovos and G. Kostopoulos: Greater contribution of N-methyl-D-aspartic acid receptors in ventral compared to dorsal hippocampal slices in the expression and long-term maintenance of epileptiform activity. *Neuroscience*, 135(3), 765–79 (2005)

141. C. Papatheodoropoulos: NMDA receptor-dependent high-frequency network oscillations (100–300 Hz) in rat hippocampal slices. *Neurosci Lett*, 414(3), 197–202 (2007)

142. C. Moschovos, G. Kostopoulos and C. Papatheodoropoulos: Endogenous adenosine induces NMDA receptor-independent persistent epileptiform discharges in dorsal and ventral hippocampus via activation of A2 receptors. *Epilepsy Res*, 100(1–2), 157–67 (2012)

143. C. Papatheodoropoulos: Higher intrinsic network excitability in ventral compared with the dorsal hippocampus is controlled less effectively by GABAB receptors. *BMC Neurosci*, 16(1), 75 (2015)
DOI: 10.1186/s12868-015-0213-z

144. A. V. Mikroulis and C. Psarropoulou: Endogenous ACh effects on NMDA-induced interictal-like discharges along the septotemporal hippocampal axis of adult rats and their modulation by an early life generalized seizure. *Epilepsia*, 53(5), 879–87 (2012)
DOI: 10.1111/j.1528-1167.2012.03440.x

145. W. M. Burnham: Primary and “transfer” seizure development in the kindled rat. *Can J Neurol Sci*, 2(4), 417–28 (1975)
DOI: 10.1017/S0317167100020564

146. E. W. Lothman and R. C. Collins: Kainic acid induced limbic seizures: metabolic, behavioral, electroencephalographic and neuropathological correlates. *Brain Res*, 218(1–2), 299–318 (1981)
DOI: 10.1016/0006-8993(81)91308-1

147. D. C. McIntyre, D. Nathanson and N. Edson: A new model of partial status epilepticus based on kindling. *Brain Res*, 250(1), 53–63 (1982)
DOI: 10.1016/0006-8993(82)90952-0

148. A. Becker, K. Letzel, U. Letzel and G. Grecksch: Kindling of the dorsal and the ventral hippocampus: effects on learning performance in rats. *Physiol Behav*, 62(6), 1265–71 (1997)
DOI: 10.1016/S0031-9384(97)00303-X

149. K. Akaike, S. Tanaka, H. Tojo, S. Fukumoto, S. Imamura and M. Takigawa: Kainic acid-induced dorsal and ventral hippocampal seizures in rats. *Brain Res*, 900(1), 65–71 (2001)
DOI: 10.1016/S0006-8993(01)02252-1

150. U. Haussler, L. Bielefeld, U. P. Froriep, J. Wolfart and C. A. Haas: Septotemporal position in the hippocampal formation determines epileptic and neurogenic activity in temporal lobe epilepsy. *Cereb Cortex*, 22(1), 26–36 (2012)

151. B. Greco, J. Prevost and Y. Gioanni: Intracerebral microinjections of dermorphin: search for the epileptic induction thresholds. *Neuroreport*, 5(16), 2169–72 (1994)
DOI: 10.1097/00001756-199410270-00045

152. E. W. Lothman and J. M. Williamson: Influence of electrical stimulus parameters on afterdischarge thresholds in the rat hippocampus. *Epilepsy Res*, 13(3), 205–13 (1992)
DOI: 10.1016/0920-1211(92)90054-W

153. C. A. Carrington, K. L. Gilby and D. C. McIntyre: Effect of focal low-frequency stimulation on amygdala-kindled afterdischarge thresholds and seizure profiles in fast- and slow-kindling rat strains. *Epilepsia*, 48(8), 1604–13 (2007)

154. R. Racine, P. A. Rose and W. M. Burnham: Afterdischarge thresholds and kindling rates in dorsal and ventral hippocampus and dentate gyrus. *Can J Neurol Sci*, 4(4), 273–8 (1977)
DOI: 10.1017/S0317167100025117

155. M. Lerner-Natoli, G. Rondouin and M. Baldy-Moulinier: Hippocampal kindling in the rat: intrastructural differences. *J Neurosci Res*, 12(1), 101–11 (1984) doi:10.1.002/jnr.490120110

156. C. N. Filipe, J. P. Pijn, V. M. de Lima and F. H. da Silva: Propagation of afterdischarges along the septo-temporal axis of the rat hippocampus: a quantitative analysis. *Electroencephalogr Clin Neurophysiol*, 73(2), 172–8 (1989)
DOI: 10.1016/0013-4694(89)90198-3

157. K. Yoshida: Influences of bilateral hippocampal lesions upon kindled amygdaloid convulsive seizure in rats. *Physiol Behav*, 32(1), 123–6 (1984) DOI: 10.1016/0031-9384(84)90082-9

158. S. Imamura, S. Tanaka, K. Akaike, H. Tojo, M. Takigawa and J. Kuratsu: Hippocampal transection attenuates kainic acid-induced amygdalar seizures in rats. *Brain Res*, 897(1–2), 93–103 (2001) DOI: 10.1016/S0006-8993(01)02098-4

159. S. Osawa, M. Iwasaki, R. Hosaka, Y. Matsuzaka, H. Tomita, T. Ishizuka, E. Sugano, E. Okumura, H. Yawo, N. Nakasato, T. Tominaga and H. Mushiake: Optogenetically induced seizure and the longitudinal hippocampal network dynamics. *PLoS One*, 8(4), e60928 (2013) DOI: 10.1371/journal.pone.0060928

160. L. W. Swanson, J. M. Wyss and W. M. Cowan: An autoradiographic study of the organization of intrahippocampal association pathways in the rat. *J Comp Neurol*, 181(4), 681–715 (1978)

161. X. G. Li, P. Somogyi, A. Ylinen and G. Buzsaki: The hippocampal CA3 network: an *in vivo* intracellular labeling study. *J Comp Neurol*, 339(2), 181–208 (1994)

162. S. Yang, S. Yang, T. Moreira, G. Hoffman, G. C. Carlson, K. J. Bender, B. E. Alger and C. M. Tang: Interlamellar CA1 network in the hippocampus. *Proc Natl Acad Sci U S A*, 111(35), 12919–24 (2014)

163. N. Ishizuka, J. Weber and D. G. Amaral: Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. *J Comp Neurol*, 295(4), 580–623 (1990) DOI: 10.1002/cne.902950407

164. A. Sik, M. Penttonen and G. Buzsaki: Interneurons in the hippocampal dentate gyrus: an *in vivo* intracellular study. *Eur J Neurosci*, 9(3), 573–88 (1997) DOI: 10.1111/j.1460-9568.1997.tb01634.x

165. J. Pallud, U. Haussler, M. Langlois, S. Hamelin, B. Devaux, C. Deransart and A. Depaulis: Dentate gyrus and hilus transection blocks seizure propagation and granule cell dispersion in a mouse model for mesial temporal lobe epilepsy. *Hippocampus*, 21(3), 334–43 (2011)

166. T. J. Teyler and P. DiScenna: Long-term potentiation. *Annu Rev Neurosci*, 10, 131–61 (1987) DOI:10.1146/annurev.ne.10.030187.001023

167. T. J. Teyler, S. L. Morgan, R. N. Russell and B. L. Woodside: Synaptic plasticity and secondary epileptogenesis. *Int Rev Neurobiol*, 45, 253–67 (2001) DOI: 10.1016/S0074-7742(01)45014-8

168. T. Sutula and O. Steward: Facilitation of kindling by prior induction of long-term potentiation in the perforant path. *Brain Res*, 420(1), 109–17 (1987) DOI: 10.1016/0006-8993(87)90245-9

169. D. Kullmann: Synaptic Function. In: *The Hippocampus Book*. Ed P. Andersen, R. Morris, D. Amaral, T. Bliss&J. O'Keefe. Oxford University Press, Oxford (2007)

170. M. Hollmann and S. Heinemann: Cloned glutamate receptors. *Annu Rev Neurosci*, 17, 31–108 (1994) DOI:10.1146/annurev.ne.17.030194.000335

171. D. J. Sheffler, K. J. Gregory, J. M. Rook and P. J. Conn: Allosteric modulation of metabotropic glutamate receptors. *Adv Pharmacol*, 62, 37–77 (2011) DOI: 10.1016/B978-0-12-385952-5.00010-5

172. M. A. Desai and P. J. Conn: Excitatory effects of ACPD receptor activation in the hippocampus are mediated by direct effects on pyramidal cells and blockade of synaptic inhibition. *J Neurophysiol*, 66(1), 40–52 (1991)

173. R. W. t. Gereau and P. J. Conn: Roles of specific metabotropic glutamate receptor subtypes in regulation of hippocampal CA1 pyramidal cell excitability. *J Neurophysiol*, 74(1), 122–9 (1995)

174. R. W. t. Gereau and P. J. Conn: Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1. *J Neurosci*, 15(10), 6879–89 (1995)

175. G. Mannaioni, M. J. Marino, O. Valenti, S. F. Traynelis and P. J. Conn: Metabotropic glutamate receptors 1 and 5 differentially

regulate CA1 pyramidal cell function. *J Neurosci*, 21(16), 5925–34 (2001)

176. D. G. Amaral and P. Lavenex: Hippocampal Neuroanatomy. In: *The Hippocampus Book*. Ed P. Andersen, R. Morris, D. Amaral, T. Bliss&J. O'Keefe. Oxford University Press, Oxford (2007)

177. C. Papatheodoropoulos and G. Kostopoulos: Decreased ability of rat temporal hippocampal CA1 region to produce long-term potentiation. *Neurosci Lett*, 279(3), 177–80 (2000) DOI: 10.1016/S0304-3940(99)01002-2

178. H. Pofantis and C. Papatheodoropoulos: The alpha5GABAA receptor modulates the induction of long-term potentiation at ventral but not dorsal CA1 hippocampal synapses. *Synapse*, 68(9), 394–401 (2014)

179. S. Kouvaros and C. Papatheodoropoulos: Theta burst stimulation-induced LTP: Differences and similarities between the dorsal and ventral CA1 hippocampal synapses. *Hippocampus* (2016)

180. N. Maggio and M. Segal: Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. *J Neurosci*, 27(21), 5757–65 (2007) DOI: 10.1523/JNEUROSCI.0155-07.2007

181. G. Grigoryan, E. Korkotian and M. Segal: Selective facilitation of LTP in the ventral hippocampus by calcium stores. *Hippocampus*, 22(7), 1635–44 (2012)

182. D. Johnston, S. Wu and R. Gray: Foundations of cellular neurophysiology. In: MIT Press Cambridge MA USA, (1995)

183. P. Andersen, H. Silfvenius, S. H. Sundberg and O. Sveen: A comparison of distal and proximal dendritic synapses on CAi pyramids in guinea-pig hippocampal slices *in vitro*. *J Physiol*, 307, 273–99 (1980) DOI: 10.1113/jphysiol.1980.sp013435

184. I. D. Forsythe and G. L. Westbrook: Slow excitatory postsynaptic currents mediated by N-methyl-D-aspartate receptors on cultured mouse central neurones. *J Physiol*, 396, 515–33 (1988) DOI: 10.1113/jphysiol.1988.sp016975

185. T. Nathan, M. S. Jensen and J. D. Lambert: GABAB receptors play a major role in paired-pulse facilitation in area CA1 of the rat hippocampus. *Brain Res*, 531(1–2), 55–65 (1990) DOI: 10.1016/0006-8993(90)90757-3

186. C. Papatheodoropoulos: Striking differences in synaptic facilitation along the dorsoventral axis of the hippocampus. *Neuroscience*, 301, 454–70 (2015) DOI: 10.1016/j.neuroscience.2015.06.029

187. C. Papatheodoropoulos and G. Kostopoulos: Dorsal-ventral differentiation of short-term synaptic plasticity in rat CA1 hippocampal region. *Neurosci Lett*, 286(1), 57–60 (2000) DOI: 10.1016/S0304-3940(00)01084-3

188. S. Kouvaros and C. Papatheodoropoulos: Major dorsoventral differences in the modulation of the local CA1 hippocampal network by NMDA, mGlu5, adenosine A2A and cannabinoid CB1 receptors. *Neuroscience*, 317, 47–64 (2016) DOI: 10.1016/j.neuroscience.2015.12.059

189. C. Papatheodoropoulos and S. Kouvaros: High-frequency stimulation-induced synaptic potentiation in dorsal and ventral CA1 hippocampal synapses: the involvement of NMDA receptors, mGluR5, and (L-type) voltage-gated calcium channels. *Learn Mem*, 23(9), 460–4 (2016)

190. N. Maggio and M. Segal: Unique regulation of long term potentiation in the rat ventral hippocampus. *Hippocampus*, 17(1), 10–25 (2007)

191. G. Grigoryan and M. Segal: Ryanodine-mediated conversion of STP to LTP is lacking in synaptopodin-deficient mice. *Brain Struct Funct* (2015)

192. G. Milior, M. A. Castro, L. P. Sciarria, S. Garofalo, I. Branchi, D. Ragozzino, C. Limatola and L. Maggi: Electrophysiological Properties of CA1 Pyramidal Neurons along the Longitudinal Axis of the Mouse Hippocampus. *Sci Rep*, 6, 38242 (2016)

193. W. E. Babiec, S. A. Jami, R. Guglietta, P. B. Chen and T. J. O'Dell: Differential Regulation of NMDA Receptor-Mediated Transmission by SK Channels Underlies Dorsal-Ventral Differences in Dynamics of Schaffer Collateral Synaptic Function. *J Neurosci* (2017)

194. M. Andreasen, J. D. Lambert and M. S. Jensen: Effects of new non-N-methyl-D-aspartate antagonists on synaptic transmission in the *in vitro* rat hippocampus. *J Physiol*, 414, 317–36 (1989)
DOI: 10.1113/jphysiol.1989.sp017690

195. C. Pandis, E. Sotiriou, E. Kouvaras, E. Asprodini, C. Papatheodoropoulos and F. Angelatou: Differential expression of NMDA and AMPA receptor subunits in rat dorsal and ventral hippocampus. *Neuroscience*, 140(1), 163–75 (2006)

196. H. Monyer, N. Burnashev, D. J. Laurie, B. Sakmann and P. H. Seeburg: Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron*, 12(3), 529–40 (1994)
DOI: 10.1016/0896-6273(94)90210-0

197. J. Nabekura, T. Ueno, S. Katsurabayashi, A. Furuta, N. Akaike and M. Okada: Reduced NR2A expression and prolonged decay of NMDA receptor-mediated synaptic current in rat vagal motoneurons following axotomy. *J Physiol*, 539(Pt 3), 735–41 (2002)
DOI: 10.1113/jphysiol.2001.013379

198. N. Gu, J. Jackson, R. Goutagny, G. Lowe, F. Manseau and S. Williams: NMDA-dependent phase synchronization between septal and temporal CA3 hippocampal networks. *J Neurosci*, 33(19), 8276–87 (2013)

199. J. Kenney and D. Manahan-Vaughan: NMDA receptor-dependent synaptic plasticity in dorsal and intermediate hippocampus exhibits distinct frequency-dependent profiles. *Neuropharmacology*, 74, 108–18 (2013)
DOI: 10.1016/j.neuropharm.2013.02.017

200. H. Pofantis, P. Georgopoulos, T. Petrides and C. Papatheodoropoulos: Differences in paired-pulse inhibition and facilitation in the dentate gyrus and CA3 field between dorsal and ventral rat hippocampus. *Brain Res*, 1608, 21–30 (2015)
DOI: 10.1016/j.brainres.2015.03.003

201. C. Moschovos and C. Papatheodoropoulos: The L-type voltage-dependent calcium channel long-term potentiation is higher in the dorsal compared with the ventral associational/commissural CA3 hippocampal synapses. *Neurosci Res*, 106, 62–5 (2016)
DOI: 10.1016/j.neures.2015.10.008

202. C. Papatheodoropoulos, E. Asprodini, I. Nikita, C. Koutsona and G. Kostopoulos: Weaker synaptic inhibition in CA1 region of ventral compared to dorsal rat hippocampal slices. *Brain Res*, 948(1–2), 117–21 (2002)
DOI: 10.1016/S0006-8993(02)02958-X

203. T. Petrides, P. Georgopoulos, G. Kostopoulos and C. Papatheodoropoulos: The GABAA receptor-mediated recurrent inhibition in ventral compared with dorsal CA1 hippocampal region is weaker, decays faster and lasts less. *Exp Brain Res*, 177(3), 370–83 (2007)

204. P. Georgopoulos, T. Petrides, G. Kostopoulos and C. Papatheodoropoulos: Varying magnitude of GABAergic recurrent inhibition enhancement by different sedative/anesthetic agents in dorsal and ventral hippocampus. *Brain Res*, 1207, 43–59 (2008)
DOI: 10.1016/j.brainres.2008.02.017

205. R. Dingledine and G. Somjen: Calcium dependence of synaptic transmission in the hippocampal slice. *Brain Res*, 207(1), 218–22 (1981)
DOI: 10.1016/0006-8993(81)90697-1

206. M. Balestrino, P. G. Aitken and G. G. Somjen: The effects of moderate changes of extracellular K+ and Ca2+ on synaptic and neural function in the CA1 region of the hippocampal slice. *Brain Res*, 377(2), 229–39 (1986)
DOI: 10.1016/0006-8993(86)90863-2

207. B. Katz and R. Miledi: Tetrodotoxin-resistant electric activity in presynaptic terminals. *J Physiol*, 203(2), 459–87 (1969)
DOI: 10.1113/jphysiol.1969.sp008875

208. L. G. Wu and P. Saggau: Presynaptic calcium is increased during normal synaptic transmission and paired-pulse facilitation, but not in long-term potentiation in area CA1 of hippocampus. *J Neurosci*, 14(2), 645–54 (1994)

209. Y. Goda and C. F. Stevens: Two components of transmitter release at a central synapse. *Proc Natl Acad Sci U S A*, 91(26), 12942–6 (1994)
DOI: 10.1073/pnas.91.26.12942

210. W. A. Catterall: Structure and function of neuronal Ca^{2+} channels and their role in neurotransmitter release. *Cell Calcium*, 24(5–6), 307–23 (1998)
DOI: 10.1016/S0143-4160(98)90055-0

211. D. Debanne, N. C. Guerineau, B. H. Gahwiler and S. M. Thompson: Paired-pulse facilitation and depression at unitary synapses in rat hippocampus: quantal fluctuation affects subsequent release. *J Physiol*, 491 (Pt 1), 163–76 (1996)
DOI: 10.1113/jphysiol.1996.sp021204

212. T. Manabe, D. J. Wyllie, D. J. Perkel and R. A. Nicoll: Modulation of synaptic transmission and long-term potentiation: effects on paired pulse facilitation and EPSC variance in the CA1 region of the hippocampus. *J Neurophysiol*, 70(4), 1451–9 (1993)

213. L. E. Dobrunz and C. F. Stevens: Heterogeneity of release probability, facilitation, and depletion at central synapses. *Neuron*, 18(6), 995–1008 (1997)
DOI: 10.1016/S0896-6273(00)80338-4

214. S. M. Thompson, M. Capogna and M. Scanziani: Presynaptic inhibition in the hippocampus. *Trends Neurosci*, 16(6), 222–7 (1993)
DOI: 10.1016/0166-2236(93)90160-N

215. K. W. Yoon and S. M. Rothman: Adenosine inhibits excitatory but not inhibitory synaptic transmission in the hippocampus. *J Neurosci*, 11(5), 1375–80 (1991)

216. O. J. Manzoni, T. Manabe and R. A. Nicoll: Release of adenosine by activation of NMDA receptors in the hippocampus. *Science*, 265(5181), 2098–101 (1994)
DOI: 10.1126/science.7916485

217. S. J. Potashner: Baclofen: effects on amino acid release and metabolism in slices of guinea pig cerebral cortex. *J Neurochem*, 32(1), 103–9 (1979)
DOI: 10.1111/j.1471-4159.1979.tb04516.x

218. P. C. Waldmeier, P. Wicki, J. J. Feldtrauer, S. J. Mickel, H. Bittiger and P. A. Baumann: GABA and glutamate release affected by GABAB receptor antagonists with similar potency: no evidence for pharmacologically different presynaptic receptors. *Br J Pharmacol*, 113(4), 1515–21 (1994)
DOI: 10.1111/j.1476-5381.1994.tb17168.x

219. J. R. Chalifoux and A. G. Carter: GABAB receptor modulation of synaptic function. *Curr Opin Neurobiol*, 21(2), 339–44 (2011)

220. M. Kano: Control of synaptic function by endocannabinoid-mediated retrograde signaling. *Proc Jpn Acad Ser B Phys Biol Sci*, 90(7), 235–50 (2014)
DOI: 10.2183/pjab.90.235

221. F. Steindel, R. Lerner, M. Haring, S. Ruehle, G. Marsicano, B. Lutz and K. Monory: Neuron-type specific cannabinoid-mediated G protein signalling in mouse hippocampus. *J Neurochem*, 124(6), 795–807 (2013)

222. K. Monory, H. Blaudzun, F. Massa, N. Kaiser, T. Lemberger, G. Schutz, C. T. Wotjak, B. Lutz and G. Marsicano: Genetic dissection of behavioural and autonomic effects of Delta(9)-tetrahydrocannabinol in mice. *PLoS Biol*, 5(10), e269 (2007)
DOI: 10.1371/journal.pbio.0050269

223. K. S. Lee, M. Reddington, P. Schubert and G. Kreutzberg: Regulation of the strength of adenosine modulation in the hippocampus by a differential distribution of the density of A1 receptors. *Brain Res*, 260(1), 156–9 (1983)
DOI: 10.1016/0006-8993(83)90779-5

224. D. J. Sheffler, A. B. Pinkerton, R. Dahl, A. Markou and N. D. Cosford: Recent progress in the synthesis and characterization of group II metabotropic glutamate receptor allosteric modulators. *ACS Chem Neurosci*, 2(8), 382–93 (2011)

225. R. Anwyl: Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Res Brain Res Rev*, 29(1), 83–120 (1999)
DOI: 10.1016/S0165-0173(98)00050-2

226. M. T. Tebano, A. Martire, N. Rebola, R. Pepponi, M. R. Domenici, M. C. Gro, M. A. Schwarzschild, J. F. Chen, R. A. Cunha and P. Popoli: Adenosine A2A receptors and metabotropic glutamate 5 receptors are co-localized and functionally interact in the hippocampus: a possible key mechanism in the modulation of N-methyl-D-aspartate effects. *J Neurochem*, 95(4), 1188–200 (2005)

227. A. J. Doherty, M. J. Palmer, J. M. Henley, G. L. Collingridge and D. E. Jane: (RS)-

2-chloro-5-hydroxyphenylglycine (CHPG) activates mGlu5, but no mGlu1, receptors expressed in CHO cells and potentiates NMDA responses in the hippocampus. *Neuropharmacology*, 36(2), 265–7 (1997) DOI: 10.1016/S0028-3908(97)00001-4

228. A. M. Sebastiao and J. A. Ribeiro: Tuning and fine-tuning of synapses with adenosine. *Curr Neuropharmacol*, 7(3), 180–94 (2009)

229. B. E. Alger: Gating of GABAergic inhibition in hippocampal pyramidal cells. *Ann N Y Acad Sci*, 627, 249–63 (1991) DOI: 10.1111/j.1749-6632.1991.tb25929.x

230. M. Farrant and K. Kaila: The cellular, molecular and ionic basis of GABA(A) receptor signalling. *Prog Brain Res*, 160, 59–87 (2007) DOI: 10.1016/S0079-6123(06)60005-8

231. E. R. Korpi, G. Grunder and H. Luddens: Drug interactions at GABA(A) receptors. *Prog Neurobiol*, 67(2), 113–59 (2002)

232. J. S. Isaacson, J. M. Solis and R. A. Nicoll: Local and diffuse synaptic actions of GABA in the hippocampus. *Neuron*, 10(2), 165–75 (1993)

233. D. J. Rossi, M. Hamann and D. Attwell: Multiple modes of GABAergic inhibition of rat cerebellar granule cells. *J Physiol*, 548(Pt 1), 97–110 (2003)

234. W. Wei, N. Zhang, Z. Peng, C. R. Houser and I. Mody: Perisynaptic localization of delta subunit-containing GABA(A) receptors and their activation by GABA spillover in the mouse dentate gyrus. *J Neurosci*, 23(33), 10650–61 (2003)

235. D. M. Kullmann, A. Ruiz, D. M. Rusakov, R. Scott, A. Semyanov and M. C. Walker: Presynaptic, extrasynaptic and axonal GABAA receptors in the CNS: where and why? *Prog Biophys Mol Biol*, 87(1), 33–46 (2005)

236. A. Semyanov, M. C. Walker, D. M. Kullmann and R. A. Silver: Tonically active GABA A receptors: modulating gain and maintaining the tone. *Trends Neurosci*, 27(5), 262–9 (2004)

237. V. B. Caraiscos, E. M. Elliott, K. E. You-Ten, V. Y. Cheng, D. Belelli, J. G. Newell, M. F. Jackson, J. J. Lambert, T. W. Rosahl, K. A. Wafford, J. F. MacDonald and B. A. Orser: Tonic inhibition in mouse hippocampal CA1 pyramidal neurons is mediated by alpha5 subunit-containing gamma-aminobutyric acid type A receptors. *Proc Natl Acad Sci U S A*, 101(10), 3662–7 (2004)

238. J. Glykys and I. Mody: Hippocampal network hyperactivity after selective reduction of tonic inhibition in GABA A receptor alpha5 subunit-deficient mice. *J Neurophysiol*, 95(5), 2796–807 (2006)

239. R. P. Bonin, L. J. Martin, J. F. MacDonald and B. A. Orser: Alpha5GABAA receptors regulate the intrinsic excitability of mouse hippocampal pyramidal neurons. *J Neurophysiol*, 98(4), 2244–54 (2007)

240. P. Somogyi and T. Klausberger: Defined types of cortical interneurone structure space and spike timing in the hippocampus. *J. Physiol.*, 562(Pt 1), 9–26 (2005)

241. E. Sigel and M. E. Steinmann: Structure, function, and modulation of GABA(A) receptors. *J Biol Chem*, 287(48), 40224–31 (2012)

242. B. G. Gunn, L. Cunningham, S. G. Mitchell, J. D. Swinny, J. J. Lambert and D. Belelli: GABAA receptor-acting neurosteroids: a role in the development and regulation of the stress response. *Front Neuroendocrinol*, 36, 28–48 (2015) DOI: 10.1016/j.yfrne.2014.06.001

243. N. Maggio and M. Segal: Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. *J Neurosci*, 29(9), 2857–66 (2009)

244. M. A. Wilson: GABA physiology: modulation by benzodiazepines and hormones. *Crit Rev Neurobiol*, 10(1), 1–37 (1996) DOI: 10.1615/CritRevNeurobiol.v10.i1.10

245. E. Sotiriou, C. Papatheodoropoulos and F. Angelatou: Differential expression of gamma-aminobutyric acid--a receptor subunits in rat dorsal and ventral hippocampus. *J Neurosci Res*, 82(5), 690–700 (2005)

246. K. Sarantis, E. Sotiriou, C. Papatheodoropoulos, N. Matsokis and F. Angelatou: Differential pharmacological properties of GABAA/benzodiazepine receptor complex in dorsal compared to ventral rat hippocampus. *Neurochem Int*, 52(6), 1019–29 (2008)

247. S. Vicini, C. Ferguson, K. Prybylowski, J. Kralic, A. L. Morrow and G. E. Homanics: GABA(A) receptor alpha1 subunit deletion prevents developmental changes of inhibitory synaptic currents in cerebellar neurons. *J Neurosci*, 21(9), 3009–16 (2001)

248. S. Pirker, C. Schwarzer, A. Wieselthaler, W. Sieghart and G. Sperk: GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience*, 101(4), 815–50 (2000)

249. C. Sur, L. Fresu, O. Howell, R. M. McKernan and J. R. Atack: Autoradiographic localization of alpha5 subunit-containing GABAA receptors in rat brain. *Brain Res*, 822(1–2), 265–70 (1999)

250. A. Scimemi, A. Semyanov, G. Sperk, D. M. Kullmann and M. C. Walker: Multiple and plastic receptors mediate tonic GABAA receptor currents in the hippocampus. *J Neurosci*, 25(43), 10016–24 (2005)

251. H. Hortnagl, M. L. Berger, G. Sperk and C. Pifl: Regional heterogeneity in the distribution of neurotransmitter markers in the rat hippocampus. *Neuroscience*, 45(2), 261–72 (1991)
DOI: 10.1016/0306-4522(91)90224-C

252. C. L. Padgett and P. A. Slesinger: GABAB Receptor Coupling to G-proteins and Ion Channels. In: *Advances in Pharmacology*. Ed P. B. Thomas. Academic Press, (2010)

253. M. Gassmann and B. Bettler: Regulation of neuronal GABA(B) receptor functions by subunit composition. *Nat Rev Neurosci*, 13(6), 380–94 (2012)

254. S. Kantamneni, I. M. Gonzalez-Gonzalez, J. Luo, H. Cimarosti, S. C. Jacobs, N. Jaafari and J. M. Henley: Differential regulation of GABAB receptor trafficking by different modes of N-methyl-D-aspartate (NMDA) receptor signaling. *J Biol Chem*, 289(10), 6681–94 (2014)

255. C. H. Davies, S. J. Starkey, M. F. Pozza and G. L. Collingridge: GABA autoreceptors regulate the induction of LTP. *Nature*, 349(6310), 609–11 (1991)

256. D. D. Mott and D. V. Lewis: Facilitation of the induction of long-term potentiation by GABAB receptors. *Science*, 252(5013), 1718–20 (1991)
DOI: 10.1126/science.1675489

257. C. H. Davies and G. L. Collingridge: Regulation of EPSPs by the synaptic activation of GABAB autoreceptors in rat hippocampus. *J Physiol*, 496 (Pt 2), 451–70 (1996)
DOI: 10.1113/jphysiol.1996.sp021698

258. J. Larson, D. Wong and G. Lynch: Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res*, 368(2), 347–50 (1986)
DOI: 10.1016/0006-8993(86)90579-2

259. C. H. Davies, S. N. Davies and G. L. Collingridge: Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. *J Physiol*, 424, 513–31 (1990)
DOI: 10.1113/jphysiol.1990.sp018080

260. E. R. Kandel and W. A. Spencer: Cellular neurophysiological approaches in the study of learning. *Physiol Rev*, 48(1), 65–134 (1968)

261. N. Tsukahara: Synaptic plasticity in the mammalian central nervous system. *Annu Rev Neurosci*, 4, 351–79 (1981)
DOI:10.1146/annurev.ne.04.030181.002031

262. H. Anwar, X. Li, D. Bucher and F. Nadim: Functional roles of short-term synaptic plasticity with an emphasis on inhibition. *Curr Opin Neurobiol*, 43, 71–78 (2017)
DOI: 10.1016/j.conb.2017.01.002

263. S. J. Martin and R. G. Morris: New life in an old idea: the synaptic plasticity and memory hypothesis revisited. *Hippocampus*, 12(5), 609–36 (2002)

264. R. S. Zucker and W. G. Regehr: Short-term synaptic plasticity. *Annu Rev Physiol*, 64, 355–405 (2002)
DOI: 10.1146/annurev.physiol.64.092501.114547

265. M. Raastad and R. Lipowski: Diversity of postsynaptic amplitude and failure probability of unitary excitatory synapses between CA3 and CA1 cells in the rat hippocampus. *Eur J Neurosci*, 8(6), 1265–74 (1996)
DOI: 10.1111/j.1460-9568.1996.tb01295.x

266. N. A. Hessler, A. M. Shirke and R. Malinow: The probability of transmitter release at a mammalian central synapse. *Nature*, 366(6455), 569–72 (1993)

267. C. Allen and C. F. Stevens: An evaluation of causes for unreliability of synaptic transmission. *Proc Natl Acad Sci U S A*, 91(22), 10380–3 (1994)
DOI: 10.1073/pnas.91.22.10380

268. V. N. Murthy, T. J. Sejnowski and C. F. Stevens: Heterogeneous release properties of visualized individual hippocampal synapses. *Neuron*, 18(4), 599–612 (1997)
DOI: 10.1016/S0896-6273(00)80301-3

269. C. Rosenmund, J. D. Clements and G. L. Westbrook: Nonuniform probability of glutamate release at a hippocampal synapse. *Science*, 262(5134), 754–7 (1993)
DOI: 10.1126/science.7901909

270. M. Raastad, J. F. Storm and P. Andersen: Putative Single Quantum and Single Fibre Excitatory Postsynaptic Currents Show Similar Amplitude Range and Variability in Rat Hippocampal Slices. *Eur J Neurosci*, 4(1), 113–117 (1992)
DOI: 10.1111/j.1460-9568.1992.tb00114.x

271. B. Katz and R. Miledi: The role of calcium in neuromuscular facilitation. *J Physiol*, 195(2), 481–92 (1968)
DOI: 10.1113/jphysiol.1968.sp008469

272. O. Prange and T. H. Murphy: Correlation of miniature synaptic activity and evoked release probability in cultures of cortical neurons. *J Neurosci*, 19(15), 6427–38 (1999)

273. K. Maruki, Y. Izaki, M. Nomura and T. Yamauchi: Differences in paired-pulse facilitation and long-term potentiation between dorsal and ventral CA1 regions in anesthetized rats. *Hippocampus*, 11(6), 655–61 (2001)

274. S. L. Jackman, J. Turecek, J. E. Belinsky and W. G. Regehr: The calcium sensor synaptotagmin 7 is required for synaptic facilitation. *Nature*, 529(7584), 88–91 (2016)

275. T. Nathan and J. D. Lambert: Depression of the fast IPSP underlies paired-pulse facilitation in area CA1 of the rat hippocampus. *J Neurophysiol*, 66(5), 1704–15 (1991)

276. R. Metherate and J. H. Ashe: Facilitation of an NMDA receptor-mediated EPSP by paired-pulse stimulation in rat neocortex via depression of GABAergic IPSPs. *J Physiol*, 481 (Pt 2), 331–48 (1994)
DOI: 10.1113/jphysiol.1994.sp020443

277. G. Buzsaki: Theta oscillations in the hippocampus. *Neuron*, 33(3), 325–40 (2002)
DOI: 10.1016/S0896-6273(02)00586-X

278. T. V. Bliss, G. L. Collingridge and R. Morris: Synaptic Plasticity in the Hippocampus. In: *The Hippocampus Book*. Ed P. Andersen, R. Morris, D. Amaral, T. Bliss & J. O'Keefe. (2007)

279. A. J. Silva: Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. *J Neurobiol*, 54(1), 224–37 (2003)

280. G. Neves, S. F. Cooke and T. V. Bliss: Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nat Rev Neurosci*, 9(1), 65–75 (2008)

281. T. Takeuchi, A. J. Duszkiewicz and R. G. Morris: The synaptic plasticity and memory hypothesis: encoding, storage and persistence. *Philos Trans R Soc Lond B Biol Sci*, 369(1633), 20130288 (2014)
DOI: 10.1098/rstb.2013.0288

282. R. Malik and D. Johnston: Dendritic GIRK channels gate the integration window, plateau potentials and induction of synaptic plasticity in dorsal but not ventral CA1 neurons. *J Neurosci* (2017)

283. N. Maggio and M. Segal: Corticosteroid regulation of synaptic plasticity in the hippocampus. *ScientificWorldJournal*, 10, 462–9 (2010)
DOI: 10.1100/tsw.2010.48

284. G. Grigoryan, Z. Ardi, A. Albrecht, G. Richter-Levin and M. Segal: Juvenile stress alters LTP in ventral hippocampal slices: involvement of noradrenergic mechanisms. *Behav Brain Res*, 278, 559–62 (2015)
DOI: 10.1016/j.bbr.2014.09.047

285. G. Grigoryan and M. Segal: Lasting Differential Effects on Plasticity Induced by Prenatal

Stress in Dorsal and Ventral Hippocampus. *Neural Plast*, 2016, 2540462 (2016)

286. G. Grigoryan and M. Segal: Prenatal stress alters noradrenergic modulation of LTP in hippocampal slices. *J Neurophysiol*, 110(2), 279–85 (2013)

287. Y. Izaki, M. Takita and M. Nomura: Comparative induction of long-term depression between dorsal and ventral hippocampal CA1 in the anesthetized rat. *Neurosci Lett*, 294(3), 171–4 (2000) DOI: 10.1016/S0304-3940(00)01570-6

288. K. A. Dougherty, T. Islam and D. Johnston: Intrinsic excitability of CA1 pyramidal neurones from the rat dorsal and ventral hippocampus. *J Physiol*, 590(Pt 22), 5707–22 (2012)

289. R. Malik, K. A. Dougherty, K. Parikh, C. Byrne and D. Johnston: Mapping the electrophysiological and morphological properties of CA1 pyramidal neurons along the longitudinal hippocampal axis. *Hippocampus*, 26(3), 341–61 (2016)

290. B. Marcelin, Z. Liu, Y. Chen, A. S. Lewis, A. Becker, S. McClelland, D. M. Chetkovich, M. Migliore, T. Z. Baram, M. Esclapez and C. Bernard: Dorsoventral differences in intrinsic properties in developing CA1 pyramidal cells. *J Neurosci*, 32(11), 3736–47 (2012)

291. C. Honigsperger, M. Marosi, R. Murphy and J. F. Storm: Dorsoventral differences in Kv7/M-current and its impact on resonance, temporal summation and excitability in rat hippocampal pyramidal cells. *J Physiol*, 593(7), 1551–80 (2015)

292. B. Marcelin, J. N. Lugo, A. L. Brewster, Z. Liu, A. S. Lewis, S. McClelland, D. M. Chetkovich, T. Z. Baram, A. E. Anderson, A. Becker, M. Esclapez and C. Bernard: Differential dorso-ventral distributions of Kv4.2. and HCN proteins confer distinct integrative properties to hippocampal CA1 pyramidal cell distal dendrites. *J Biol Chem*, 287(21), 17656–61 (2012)

293. C. S. Kim and D. Johnston: A1 adenosine receptor-mediated GIRK channels contribute to the resting conductance of CA1 neurons in the dorsal hippocampus. *J Neurophysiol*, 113(7), 2511–23 (2015)

294. K. A. Dougherty, D. A. Nicholson, L. Diaz, E. W. Buss, K. M. Neuman, D. M. Chetkovich and D. Johnston: Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from dorsal and ventral hippocampus. *J Neurophysiol*, 109(7), 1940–53 (2013)

295. R. R. Llinas: The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science*, 242(4886), 1654–64 (1988) DOI: 10.1126/science.3059497

296. H. Vacher, D. P. Mohapatra and J. S. Trimmer: Localization and targeting of voltage-dependent ion channels in mammalian central neurons. *Physiol Rev*, 88(4), 1407–47 (2008)

297. P. J. Sjostrom, E. A. Rancz, A. Roth and M. Hausser: Dendritic excitability and synaptic plasticity. *Physiol Rev*, 88(2), 769–840 (2008)

298. R. Miles and R. K. Wong: Single neurones can initiate synchronized population discharge in the hippocampus. *Nature*, 306(5941), 371–3 (1983) DOI: 10.1038/306371a0

299. L. M. de la Prida, G. Huberfeld, I. Cohen and R. Miles: Threshold behavior in the initiation of hippocampal population bursts. *Neuron*, 49(1), 131–42 (2006)

300. I. Cohen and R. Miles: Contributions of intrinsic and synaptic activities to the generation of neuronal discharges in *in vitro* hippocampus. *J Physiol*, 524 Pt 2, 485–502 (2000) DOI: 10.1111/j.1469-7793.2000.00485.x

301. B. Haider, A. Duque, A. R. Hasenstaub and D. A. McCormick: Neocortical network activity *in vivo* is generated through a dynamic balance of excitation and inhibition. *Journal of Neuroscience*, 26(17), 4535–4545 (2006) DOI: 10.1523/JNEUROSCI.5297-05.2006

302. Y. Penn, M. Segal and E. Moses: Network synchronization in hippocampal neurons. *Proc Natl Acad Sci U S A*, 113(12), 3341–6 (2016)

303. J. Csicsvari, H. Hirase, A. Czurko, A. Mamiya and G. Buzsaki: Oscillatory

coupling of hippocampal pyramidal cells and interneurons in the behaving Rat. *J Neurosci*, 19(1), 274–287 (1999)

304. T. J. Ellender, W. Nissen, L. L. Colgin, E. O. Mann and O. Paulsen: Priming of hippocampal population bursts by individual perisomatic-targeting interneurons. *J Neurosci*, 30(17), 5979–91 (2010)

305. P. Giannopoulos and C. Papatheodoropoulos: Effects of mu-opioid receptor modulation on the hippocampal network activity of sharp wave and ripples. *Br J Pharmacol*, 168(5), 1146–64 (2013)

306. S. Kouvaros, D. Kotzadimitriou and C. Papatheodoropoulos: Hippocampal sharp waves and ripples: Effects of aging and modulation by NMDA receptors and L-type Ca channels. *Neuroscience*, 298, 26–41 (2015)
DOI: 10.1016/j.neuroscience.2015.04.012

307. G. Buzsaki: Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25(10), 1073–188 (2015)

308. C. Monier, F. Chavane, P. Baudot, L. J. Graham and Y. Fregnac: Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. *Neuron*, 37(4), 663–80 (2003)
DOI: 10.1016/S0896-6273(03)00064-3

309. R. Tatti, M. S. Haley, O. K. Swanson, T. Tselha and A. Maffei: Neurophysiology and Regulation of the Balance Between Excitation and Inhibition in Neocortical Circuits. *Biol Psychiatry* (2016)

310. J. J. Chrobak and G. Buzsaki: High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. *J Neurosci*, 16(9), 3056–3066 (1996)

311. J. G. R. Jefferys, P. Jiruska, M. de Curtis and M. Avoli: Limbic Network Synchronization and Temporal Lobe Epilepsy. In: *Jasper's Basic Mechanisms of the Epilepsies*. Ed J. L. Noebels, M. Avoli, M. A. Rogawski, R. W. Olsen&A. V. Delgado-Escueta. National Center for Biotechnology Information (US) Michael A Rogawski, Antonio V Delgado-Escueta, Jeffrey L Noebels, Massimo Avoli and Richard W Olsen., Bethesda (MD) (2012)
DOI: 10.1093/med/9780199746545.003.0014

312. A. Bragin, J. Engel, Jr., C. L. Wilson, I. Fried and G. Buzsaki: High-frequency oscillations in human brain. *Hippocampus*, 9(2), 137–42 (1999)

313. R. J. Staba and A. Bragin: High-frequency oscillations and other electrophysiological biomarkers of epilepsy: underlying mechanisms. *Biomark Med*, 5(5), 545–56 (2011)

314. J. G. Jefferys, L. Menendez de la Prida, F. Wendling, A. Bragin, M. Avoli, I. Timofeev and F. H. Lopes da Silva: Mechanisms of physiological and epileptic HFO generation. *Prog Neurobiol*, 98(3), 250–64 (2012)

315. S. E. Fox and J. B. Ranck, Jr.: Electrophysiological characteristics of hippocampal complex-spike cells and theta cells. *Exp. Brain Res.*, 41(3–4), 399–410 (1981)
DOI: 10.1007/bf00238898

316. S. S. Suzuki and G. K. Smith: Burst characteristics of hippocampal complex spike cells in the awake rat. *Exp. Neurol.*, 89(1), 90–5 (1985)

317. J. B. Ranck, Jr.: Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. *Exp. Neurol.*, 41(2), 461–531 (1973)
DOI: 10.1016/0014-4886(73)90290-2

318. K. D. Harris, H. Hirase, X. Leinekugel, D. A. Henze and G. Buzsaki: Temporal interaction between single spikes and complex spike bursts in hippocampal pyramidal cells. *Neuron*, 32(1), 141–9 (2001)
DOI: 10.1016/S0896-6273(01)00447-0

319. C. Grienberger, X. Chen and A. Konnerth: NMDA receptor-dependent multidendrite Ca(2+) spikes required for hippocampal burst firing *in vivo*. *Neuron*, 81(6), 1274–81 (2014)

320. G. G. Turrigiano, K. R. Leslie, N. S. Desai, L. C. Rutherford and S. B. Nelson: Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature*, 391(6670), 892–6 (1998)

321. D. J. Schulz: Plasticity and stability in neuronal output via changes in intrinsic excitability: it's what's inside that counts. *J Exp Biol*, 209(Pt 24), 4821–7 (2006)

322. A. Maffei: Fifty shades of inhibition. *Curr Opin Neurobiol*, 43, 43–47 (2016) DOI: 10.1016/j.conb.2016.12.003

323. R. D. Traub, A. Bibbig, F. E. LeBeau, E. H. Buhl and M. A. Whittington: Cellular mechanisms of neuronal population oscillations in the hippocampus *in vitro*. *Annu Rev Neurosci*, 27, 247–78 (2004) DOI: 10.1146/annurev.neuro.27.070203.144303

324. S. R. Cobb, E. H. Buhl, K. Halasy, O. Paulsen and P. Somogyi: Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature*, 378(6552), 75–78 (1995) DOI: 10.1038/378075a0

325. E. R. Kandel, W. A. Spencer and F. J. Brinley, Jr.: Electrophysiology of hippocampal neurons. I. Sequential invasion and synaptic organization. *J Neurophysiol*, 24, 225–242 (1961)

326. F. Pouille and M. Scanziani: Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science*, 293(5532), 1159–63 (2001)

327. M. Scanziani: GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. *Neuron*, 25(3), 673–81 (2000)

328. D. J. Rossi and M. Hamann: Spillover-mediated transmission at inhibitory synapses promoted by high affinity alpha6 subunit GABA(A) receptors and glomerular geometry. *Neuron*, 20(4), 783–95 (1998) DOI: 10.1016/S0896-6273(00)81016-8

329. M. C. Walker and A. Semyanov: Regulation of excitability by extrasynaptic GABA(A) receptors. *Results Probl Cell Differ*, 44, 29–48 (2008) DOI: 10.1007/400_2007_030

330. K. Jensen, C. S. Chiu, I. Sokolova, H. A. Lester and I. Mody: GABA transporter-1 (GAT1)-deficient mice: differential tonic activation of GABAA versus GABAB receptors in the hippocampus. *J Neurophysiol*, 90(4), 2690–701 (2003)

331. W. Wisden, D. Cope, T. Klausberger, B. Hauer, S. T. Sinkkonen, V. Tretter, R. Lujan, A. Jones, E. R. Korpi, I. Mody, W. Sieghart and P. Somogyi: Ectopic expression of the GABA(A) receptor alpha6 subunit in hippocampal pyramidal neurons produces extrasynaptic receptors and an increased tonic inhibition. *Neuropharmacology*, 43(4), 530–49 (2002) DOI: 10.1016/S0028-3908(02)00151-X

332. B. Lindner, D. Gangloff, A. Longtin and J. E. Lewis: Broadband coding with dynamic synapses. *J Neurosci*, 29(7), 2076–88 (2009)

333. Z. Rotman, P. Y. Deng and V. A. Klyachko: Short-term plasticity optimizes synaptic information transmission. *J Neurosci*, 31(41), 14800–9 (2011)

334. P. Y. Deng and V. A. Klyachko: The diverse functions of short-term plasticity components in synaptic computations. *Commun Integr Biol*, 4(5), 543–8 (2011)

335. L. F. Abbott and W. G. Regehr: Synaptic computation. *Nature*, 431(7010), 796–803 (2004)

336. W. G. Regehr: Short-term presynaptic plasticity. *Cold Spring Harb Perspect Biol*, 4(7), a005702 (2012)

337. J. J. Torres and H. J. Kappen: Emerging phenomena in neural networks with dynamic synapses and their computational implications. *Front Comput Neurosci*, 7, 30 (2013)

338. A. M. Thomson: Molecular frequency filters at central synapses. *Prog Neurobiol*, 62(2), 159–96 (2000) DOI: 10.1016/S0301-0082(00)00008-3

339. V. A. Klyachko and C. F. Stevens: Excitatory and feed-forward inhibitory hippocampal synapses work synergistically as an adaptive filter of natural spike trains. *PLoS Biol*, 4(7), e207 (2006) DOI: 10.1371/journal.pbio.0040207

340. R. Rosenbaum, J. Rubin and B. Doiron: Short term synaptic depression imposes a frequency dependent filter on synaptic information transfer. *PLoS Comput Biol*, 8(6), e1002557 (2012) DOI: 10.1371/journal.pcbi.1002557

341. W. G. Regehr and C. F. Stevens: Physiology of Synaptic Transmission and Short-Term Plasticity. In: *Synapses*. Ed W. M. Cowan, T. C. Sudhof&C. F. Stevens. The Johns Hopkins University Press, Baltimore and London (2001)

342. L. E. Dobrunz and C. F. Stevens: Response of hippocampal synapses to natural stimulation patterns. *Neuron*, 22(1), 157–66 (1999)
DOI: 10.1016/S0896-6273(00)80687-X

343. J. E. Lisman: Bursts as a unit of neural information: making unreliable synapses reliable. *Trends Neurosci*, 20(1), 38–43 (1997)

344. J. S. Dittman, A. C. Kreitzer and W. G. Regehr: Interplay between facilitation, depression, and residual calcium at three presynaptic terminals. *J Neurosci*, 20(4), 1374–85 (2000)

345. L. F. Abbott, J. A. Varela, K. Sen and S. B. Nelson: Synaptic depression and cortical gain control. *Science*, 275(5297), 220–4 (1997)
DOI: 10.1126/science.275.5297.221

346. B. G. Gunn, C. D. Cox, Y. Chen, M. Frotscher, C. M. Gall, T. Z. Baram and G. Lynch: The Endogenous Stress Hormone CRH Modulates Excitatory Transmission and Network Physiology in Hippocampus. *Cereb Cortex*, 1–17 (2017)

347. H. Markram and M. Tsodyks: Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature*, 382(6594), 807–10 (1996)

348. I. Katona: Cannabis and Endocannabinoid Signaling in Epilepsy. *Handb Exp Pharmacol*, 231, 285–316 (2015)
DOI: 10.1007/978-3-319-20825-1_10

349. M. J. Wallace, J. L. Wiley, B. R. Martin and R. J. DeLorenzo: Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects. *Eur J Pharmacol*, 428(1), 51–7 (2001)
DOI: 10.1016/S0014-2999(01)01243-2

350. M. Shen and S. A. Thayer: Delta9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Mol Pharmacol*, 55(1), 8–13 (1999)

351. I. Katona and T. F. Freund: Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. *Nat Med*, 14(9), 923–30 (2008)

352. V. Rudenko, A. Rafiuddin, J. R. Leheste and L. K. Friedman: Inverse relationship of cannabimimetic (R+)WIN 55, 212 on behavior and seizure threshold during the juvenile period. *Pharmacol Biochem Behav*, 100(3), 474–84 (2012)

353. M. J. Wallace, R. E. Blair, K. W. Falenski, B. R. Martin and R. J. DeLorenzo: The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther*, 307(1), 129–37 (2003)

354. K. Monory, F. Massa, M. Egertova, M. Eder, H. Blaudzun, R. Westenbroek, W. Kelsch, W. Jacob, R. Marsch, M. Ekker, J. Long, J. L. Rubenstein, S. Goebbels, K. A. Nave, M. During, M. Klugmann, B. Wolfel, H. U. Dodt, W. Zieglgansberger, C. T. Wotjak, K. Mackie, M. R. Elphick, G. Marsicano and B. Lutz: The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron*, 51(4), 455–66 (2006)

355. A. Ameri and T. Simmet: Effects of 2-arachidonylglycerol, an endogenous cannabinoid, on neuronal activity in rat hippocampal slices. *Naunyn Schmiedebergs Arch Pharmacol*, 361(3), 265–72 (2000)
DOI: 10.1007/s002109900200

356. R. E. Blair, L. S. Deshpande, S. Sombati, K. W. Falenski, B. R. Martin and R. J. DeLorenzo: Activation of the cannabinoid type-1 receptor mediates the anticonvulsant properties of cannabinoids in the hippocampal neuronal culture models of acquired epilepsy and status epilepticus. *J Pharmacol Exp Ther*, 317(3), 1072–8 (2006)

357. P. E. Castillo, T. J. Younts, A. E. Chavez and Y. Hashimotodani: Endocannabinoid signaling and synaptic function. *Neuron*, 76(1), 70–81 (2012)

358. T. Ohno-Shosaku and M. Kano: Endocannabinoid-mediated retrograde modulation of synaptic transmission. *Curr Opin Neurobiol*, 29, 1–8 (2014)
DOI: 10.1016/j.conb.2014.03.017

Abbreviations: A_1R: adenosine A1 receptor; $A_{2A}R$: adenosine A_{2A} receptor; fEPSP: field excitatory postsynaptic potential; $GABA_AR$: γ-aminobutyric acid type A receptor; $GABA_BR$: γ-aminobutyric acid type B receptor; GIRKs: G protein-coupled inward-rectifying potassium channels; IPSC: inhibitory postsynaptic current; IPSP: inhibitory postsynaptic potential; LTP: long-term potentiation; mGluR5: metabotropic glutamate receptors type 5; NMDAR: N-methyl-D-aspartate receptor; SPW-Rs: sharp wave-ripples; VDCC: voltage-dependent calcium channels.

Key Words: Dorsoventral, Electrophysiology, Excitability, Epileptiform discharge, Facilitation, GABA, Hippocampus, *In vitro*, Long axis, LTP, Neuronal network, NMDA, Oscillation, Plasticity, Septotemporal, Sharp waves, Synaptic transmission, Theta rhythm, Review

Send correspondence to: Costas Papatheodoropoulos, Lab of Physiology, Department of Medicine, University of Patras, 26504 Rion, Patras, Greece. Tel: 030-2610-969117, Fax: 030-2610-969178, E-mail: cepapath@upatras.gr