Alpha Psychiatry

Alpha Psychiatry **2026**; 27(6): 52650
https://doi.org/10.31083/AP52650

Review

Regulation of HCN Channels by Region and Subtype in Depression and Anxiety With Mechanisms and Precision Therapy

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Academic Editor: Francesco Bartoli
Submitted: 7 April 2026 Revised: 18 June 2026 Accepted: 23 June 2026 Published: 30 October 2026

Abstract

Major depressive disorder (MDD) and anxiety disorder (AD) are the most prevalent mental disorders that account for a significant global burden of disease. Nevertheless, a considerable proportion of patients exhibit poor responsiveness to existing treatments, which has prompted research into new therapeutic targets based on the underlying pathological mechanisms. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and hyperpolarization-activated current (I_h) play key roles in regulating neuronal excitability and neural oscillations, and have attracted heightened attention in the pathogenesis of MDD and AD. However, the role of HCN channels in MDD and AD is a multifactorial one, with numerous viewpoints now being adopted that differentiate between brain regions and HCN subtypes to explore their pathogenic mechanisms and therapeutic potential. The present review comprehensively reviews the regulatory influence of HCN1–HCN4 subtypes on depressive and anxiety-like behavioral phenotypes across different related brain regions, revealing the underlying electrophysiological mechanisms through their effects on subthreshold membrane potential oscillations, action potential firing, and network oscillations. Ultimately, we discuss therapeutic potential for the treatment of depression and anxiety, targeting specific brain regions and HCN subtypes, and outline the challenges and future directions for the development of precision therapeutic strategies, including region- and subtype-selective inhibitors, targeting auxiliary proteins, ultrasound-responsive nano-drug delivery, and neuromodulation.

Keywords: HCN channels; depression; anxiety; neural oscillations; targeted therapy

Main Points

1. The effects of HCN channels on depression and anxiety are subtype- and brain region-specific.

2. By modulating subthreshold membrane potential oscillations, neuronal excitability, and network oscillations, HCN I_h constitutes a crucial electrophysiological mechanism underlying the regulation of depression and anxiety.

3. Future directions for precision intervention include region- and subtype-selective inhibitors, targeted auxiliary proteins, ultrasound-responsive nano-drug delivery, and neuromodulation.

1. Introduction

Major depressive disorder (MDD) and anxiety disorder (AD) are the most common mental disorders worldwide. Since the 1990s, MDD has consistently ranked as the leading cause of disability-adjusted life years worldwide, exerting a significant impact on the global burden of disease [1,2]. Meanwhile, AD has a higher lifetime prevalence, reaching up to 34% [3], with approximately two-thirds of people with MDD also comorbid with anxiety [4]. However, fewer than half of patients with anxiety disorders achieve a clinically significant response to first-line psychotherapy [5], up to one in three patients with MDD do not respond to current treatments and develop treatment-resistant depression [6], which highlights the importance of identifying new therapeutic targets. Moreover, the molecular mechanisms underlying the onset of depression and anxiety have not yet been fully delineated, while both depression and anxiety are associated with abnormal alterations in electrical signals in the brain within the pathway of electrochemical-electro transmission, manifesting as disturbances in neuronal resting membrane potential (RMP), dysregulation of action potential (AP) firing, and abnormalities in the integration of postsynaptic potentials. Recent research has shifted the focus to the pathological hypothesis of impaired neuronal excitability regulation, emphasizing the key role played by ion channels in this process [7,8].

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The hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are non-selective cation channels regulated by both membrane depolarization and intracellular cyclic adenosine monophosphate (cAMP). HCN channels are permeable to both Na^+ and K^+, and are activated upon membrane hyperpolarization, generating a mixed cation inward current, I_h [9]. HCN channels are widely distributed across various brain regions of the central nervous system (CNS), and I_h plays a critical role in regulating neuronal intrinsic excitability, dendritic integration, and synaptic transmission [10,11].

In recent years, numerous animal studies have shown that HCN channels and I_h are associated with depression- and anxiety-like behaviors, and it is notably that different HCN subtypes not only exhibit variations in expression and distribution across different brain regions and cell types, but also exert significantly different effects on depression- and anxiety-like phenotypes, which present challenges for the development of effective therapeutic strategies [11,12,13,14,15,16,17,18,19]. Furthermore, studies of electrophysiological mechanisms suggest that the HCN channels may influence depressive and anxiety phenotypes by regulating neuronal firing and neural network oscillations [14,15,20,21]. Although there is a wealth of literature on alterations in HCN channels subtypes in the context of depression and anxiety [11,12,13,14,15,16,17,18,19], there is still a lack of systematic integration across brain areas and subtypes. Notably, electrophysiological mechanisms provide a critical link between molecular changes and behavioral phenotypes [14,15,20,21]. However, the causal relationships at this intermediate level are not yet fully understood. In recent years, a number of intervention strategies have been developed, including subtype-selective inhibitors, auxiliary subunit targeting, and advanced delivery systems [22,23]. Nevertheless, these efforts currently lack an integrated strategic framework. To achieve these goals, this review first summarizes current knowledge on HCN channels expression and function across brain regions implicated in depression and anxiety, highlighting cross-regional and cross-subtype heterogeneity. Secondly, we discuss how HCN I_h regulates neuronal excitability and neural oscillations, and propose hypotheses for future research. Finally, we summarize the current preclinical evidence for depression/anxiety treatments that target HCN channels and outline the relevant clinical challenges and future directions.

2. Structure and Subtypes of HCN Channels

2.1 Structural Features of HCN Channels

HCN channels (Fig. 1) are tetrameric proteins belonging to the pore-loop cation channel superfamily, with each subunit comprising six transmembrane helices (S1–S6), and S1–S4 forming the voltage sensor domain (VSD) and S5–S6 forming the pore domain (PD) [24]. The intracellular C-terminus contains a C-linker and a cyclic nucleotide-binding domain (CNBD) [18]. In the absence of cAMP, the C-linker and CNBD modules act as an autoinhibitory gate, and cAMP binding relieves this inhibition to facilitate channel opening [9,25].

The HCN channel contains a unique HCN domain (HCND) at the intracellular N-terminus, adjacent to the first transmembrane segment (S1) [26]. HCND is essential for channel trafficking to the plasma membrane [27] and has been proposed to mechanically link the VSD to the C-linker [26], thereby integrating voltage-sensing and cAMP-mediated signals to regulate channel gating [27,28,29]. Furthermore, clinical genetic analyses have revealed that various genetic variants associated with HCND are linked to conditions such as epilepsy, neurodevelopmental disorders, and inappropriate sinus tachycardia [30]. To date, the full-length cryo-electron microscopy (cryo-EM) structures of human HCN1, HCN3, and HCN4 have been determined [26,31,32], but the cryo-EM structure of HCN2 has not been resolved (Fig. 2, Ref. [26,31,32,33,34]).

2.2 HCN Subtypes

Mammalian HCN channels comprise four subtypes, HCN1-HCN4, which differ in activation kinetics, cAMP sensitivity, and distribution (Table 1, Ref. [9,10,18,26,31,32,35,36,37,38,39,40,41,42]). HCN1 exhibits the fastest activation and is weakly sensitive to cAMP. HCN2 and HCN4 activate more slowly and are highly cAMP-sensitive. HCN3 shows minimal cAMP regulation [18]. Structurally, the cytoplasmic end of HCN1 features a significantly elongated S4 helix and possesses a unique filamin A-binding site located within a 22-amino acid region at the C-terminus [43], HCN3 harbors a cholesteryl hemisuccinate (CHS) binding site at the S4–S5 interface [9,32], and HCN4 has a metal ion coordination site that enhances cAMP-mediated gating [9,44].

The distribution of each subtype in the CNS exhibits regional and cell-type specificity. HCN1 is highly expressed in the neocortex, hippocampus, and cerebellum, and is enriched in the distal dendrites of cortical pyramidal neurons and at the axon terminals of parvalbumin-positive (PV+) basket cells [38,39,40,41]. HCN2 is the most widely distributed, with high expression in the thalamus and brainstem nuclei, and in cortical and subcortical structures [39]. HCN3 is expressed at low levels in the adult brain, and its role in emotional regulation remains largely unexplored [18]. HCN4 is highly expressed in the thalamus and in neurons with rhythmic firing properties, including thalamocortical relay neurons and dopaminergic neurons [10,39,42].

The subcellular localization of HCN subtypes also determines their functional roles. In pyramidal neurons, dendritic HCN1 regulates synaptic integration and plasticity, thereby influencing learning and memory [45,46]. At the axon terminals of PV+ interneurons, HCN1 increases the efficacy of gamma-aminobutyric acid (GABA) release and regulates inhibitory synaptic transmission [38]. In in-

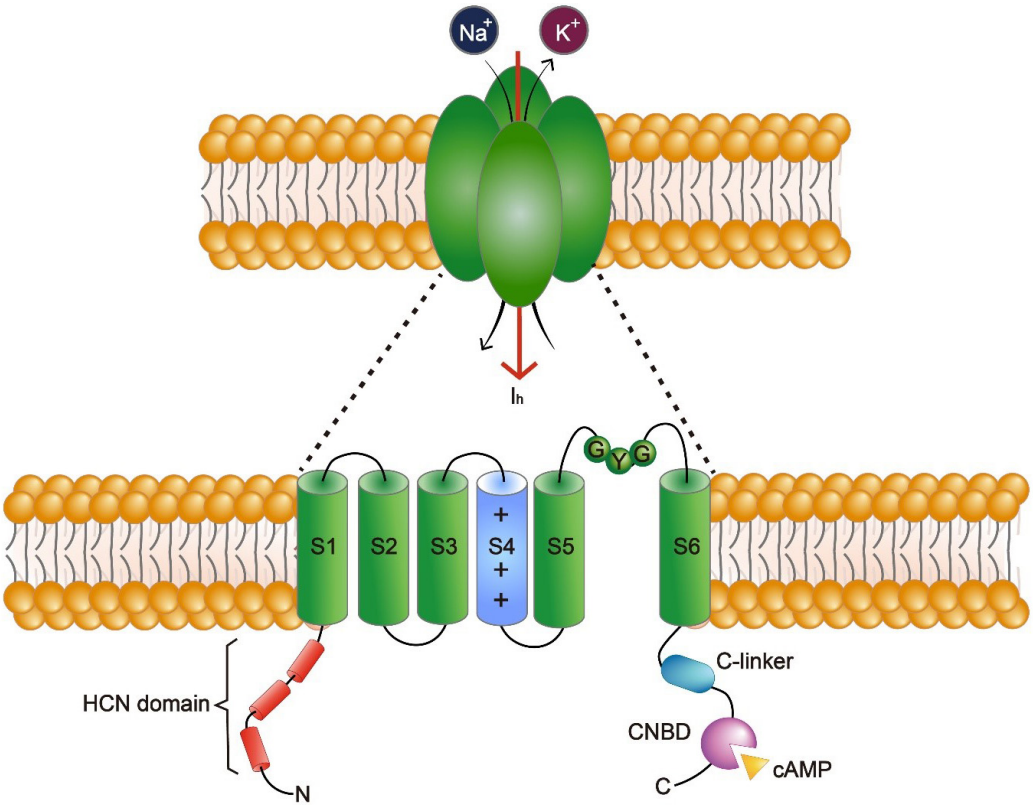


Fig. 1. Structure of HCN channel. The HCN channel forms a tetrameric central pore that is permeable to both Na^+ and K^+, generating an inward mixed cation current, I_h. Each subunit consists of six transmembrane helices, S1–S6, of which S1–S4 form the voltage sensor domain, containing the positively charged voltage sensor S4, whilst the S5–S6 helices constitute the pore domain, containing a selectivity filter possessing the glycine-tyrosine-glycine motif. The HCN domain is located at the N-terminus of the S1 helix and folds into three segmented helices. The C-linker connects the S6 helix to the CNBD. cAMP regulates HCN channel activation by binding to the CNBD at the C-terminus. HCN, hyperpolarization-activated cyclic nucleotide-gated channel; GYG, glycine-tyrosine-glycine; cAMP, cyclic adenosine monophosphate; CNBD, cyclic nucleotide-binding domain.

Table 1. Comparison of the four subtypes of HCN channels.

Subtype	Structural features	Activation kinetics	cAMP sensitivity	Expression distribution
HCN1	Filamin A binding site [43], cytoplasmically elongated S4 helix [26]	Fastest [9,18]	Weakest ($V_{0.5}$ shift of +2 to +7 mV) [35,36,37]	Neocortex: pyramidal neurons (distal dendrites and soma), hippocampus: CA1 pyramidal neurons (distal dendrites and soma), neocortex & hippocampus: PV+ basket cells (axon terminals), cerebellar cortex [38,39,40,41]
HCN2	Arginine at position 405 (R405) in the pore region [9]	Moderate [9,18]	Strong ($V_{0.5}$ shift of +10 to +25 mV) [35,36,37]	Thalamus, brainstem, neocortex: pyramidal neurons (Layer V soma) [39]
HCN3	CHS binding site [32]	Slow [9,18]	Weak ($V_{0.5}$ ~ –5 mV) [35,36,37]	Olfactory bulb, hypothalamus [18]
HCN4	Arginine at position 483 (R483) in the pore region [9], Mg^{2+} coordination site [31]	Slowest [9,18]	Strong ($V_{0.5}$ shift of +10 to +25 mV) [35,36,37]	Thalamus, medial habenula, SNc: dopaminergic neurons, basal forebrain: cholinergic projection neurons, basal ganglia: ventral pallidal neurons, olfactory bulb: mitral cells [10,39,42]

Abbreviations: HCN, hyperpolarization-activated cyclic nucleotide-gated channel; cAMP, cyclic adenosine monophosphate; SNc, substantia nigra pars compacta; CHS, cholesteryl hemisuccinate; PV, parvalbumin; CA1, cornu ammonis area 1; $V_{0.5}$, half-activation voltage.

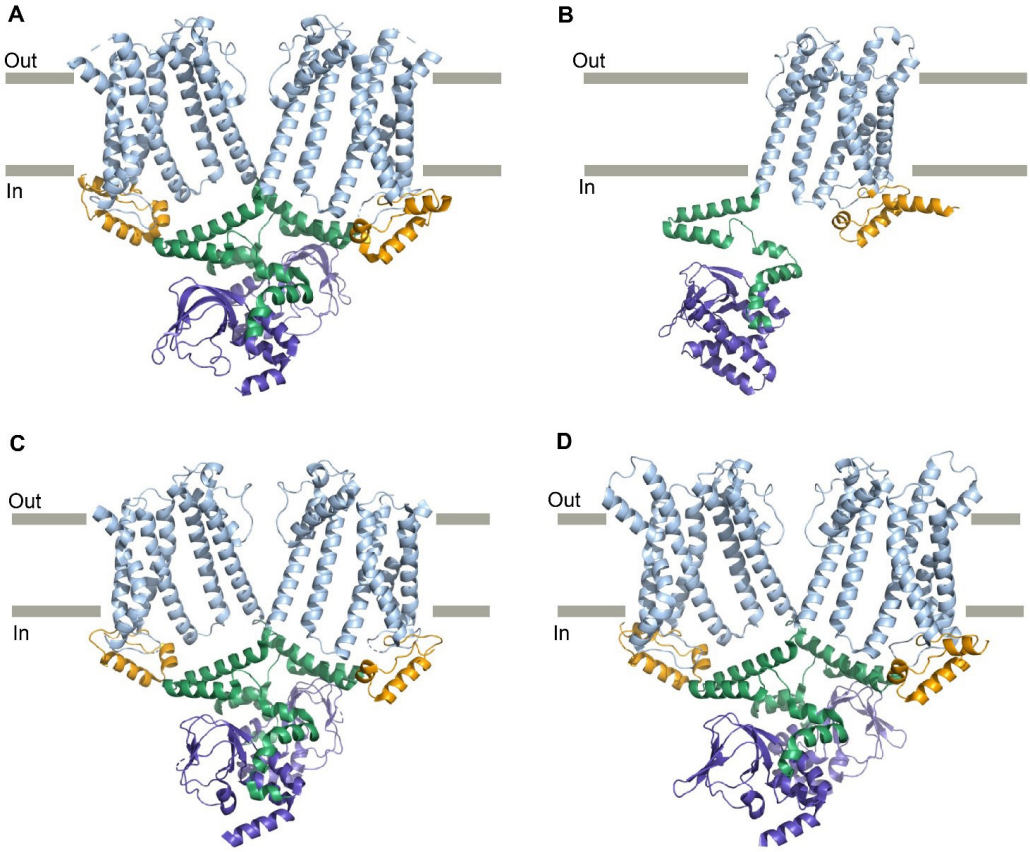


Fig. 2. Structural comparison of human HCN1-HCN4 subtypes. Cartoon representation of human HCN1 (A), HCN2 (B), HCN3 (C), and HCN4 (D). The transmembrane helix region is shown in light blue, the HCN domain in yellow, the C-linker in green, and the CNBD in purple. The structures of HCN1 (PDB ID: 5U6O, [26]), HCN3 (PDB ID: 8INZ, [32]), and HCN4 (PDB ID: 6GYN, [31]) are shown as side views of the two opposing subunits. Of note, HCN2 is a single-subunit prediction model sourced from the AlphaFold database (AlphaFold Protein Structure Database, [33,34]), rather than a cryo-EM structure. HCN, hyperpolarization-activated cyclic nucleotide-gated channel; CNBD, cyclic nucleotide-binding domain.

hibitory interneurons within the medial entorhinal cortex, hippocampus, and cerebellum, HCN1, HCN2, and HCN4 are predominantly localized in the soma and axon terminals, where they contribute to regulating RMP, neurotransmitter release, and AP firing [47,48].

3. HCN Channels and Neural Oscillations

3.1 Role of HCN I_h in Neuronal Firing

HCN channels are partially open at RMP and conduct a mixed Na^+/K^+ current, generating a net inward I_h that slightly depolarizes the neuron toward the action potential threshold [49,50,51]. At the same time, I_h increases total membrane conductance and reduces input resistance (R_{in}), producing a shunting effect that attenuates postsynaptic voltage changes [52,53,54,55]. The net impact of I_h on neuronal excitability therefore reflects a balance between depolarizing drive and shunting inhibition.

During depolarization, the slow deactivation of I_h acts as a transient outward current that may regulate the precise timing of AP firing [54]. During sustained hyperpolarization, the slow activation of I_h produces a characteristic voltage sag, followed by a rebound depolarization upon cessation of the hyperpolarizing stimulus [56]. In particular neuronal types, such as thalamocortical neurons and cholinergic interneurons, this I_h-dependent rebound depolarization is strong enough to reach the AP threshold directly, thereby driving spontaneous pacemaker activity, which constitutes the core electrophysiological mechanism underlying the intrinsic rhythmicity of these specific neuronal types [49,57,58,59,60,61].

The effect of I_h on AP firing also depends on its spatial distribution across the soma and dendrites. In pyramidal neurons of the neocortex and hippocampal CA1, the HCN1 subtype is concentrated in the distal dendrites, where it primarily attenuates and filters the amplitude and duration of excitatory postsynaptic potentials. It also accelerates the decay of inhibitory postsynaptic potentials, thus precisely regulating the summation and propagation of synaptic inputs [62,63,64]. However, in the soma and axon, I_h primarily regulates the local RMP and the recovery of the membrane potential after an AP through its sustained inward

current, thereby controlling the firing and rhythm of APs [65,66].

3.2 Role of HCN I_h in Subthreshold Oscillations in Neurons

The response preference of a neuron to the frequency of input signals is known as membrane potential resonance [67,68]. This resonant character is a band-pass filtering phenomenon, in which neurons exhibit a strongest response to input currents at specific preferred frequencies [56]. The passive membrane properties of the cell (*i.e.*, membrane capacitance and leak conductance) form a low-pass filter, and HCN channels can act as high-pass filters due to their unique kinetic properties. Collectively, these combine to form the bandpass characteristics required for resonance [56,66]. Owing to its slow kinetics, I_h opposes slow membrane potential changes but cannot respond timely at high-frequency inputs, creating a preferred resonance frequency (f_R) at which neuronal impedance peaks [9,66,69,70].

Subthreshold membrane potential oscillations (MPOs) are subthreshold regular fluctuations, the frequency of which is often closely related to the neuronal f_R [71]. I_h is the primary driver of neuronal resonance, but its slow negative feedback alone produces only voltage sag and rebound rather than sustained oscillations [56]. However, in the presence of amplifying currents such as persistent Na^+ current and T-type Ca^{2+} current, the f_R set by I_h can be amplified into self-sustained MPOs [72,73]. For instance, I_h interacts with persistent Na^+ current to generate theta-band MPOs in entorhinal stellate cells [74,75,76], while in inferior olive neurons, HCN1 sets a 3–5 Hz resonance amplified by the Cav3.1 T-type calcium channel [68]. MPOs have been shown to promote synchronized output among neurons with similar resonant properties by providing periodic temporal windows for action potential firing. This is linked to network-level rhythmic activity through ion channel kinetics [77,78].

3.3 Role of HCN I_h in Network Oscillations

Network oscillations arise from the synchronized activity of neuronal populations with similar resonance properties, which exhibit marked cell-type and regional specificity [79]. For instance, in rat thalamocortical relay neurons, I_h-mediated resonance lies within the theta frequency range (4–10 Hz) and supports the maturation of slow-wave sleep rhythms [80]. In the hippocampal CA3 region, I_h currents in pyramidal cells and basket cells predominantly mediate theta oscillations and gamma oscillations, respectively [81]. HCN channels also regulate synaptic transmission between neurons. For instance, in the hippocampal CA1 region, the HCN1 subtype is enriched at the presynaptic terminals of PV+ interneurons, where it enhances GABA release by increasing calcium influx and strengthens inhibitory synaptic transmission [38]. In larger-scale networks, the modulatory role of I_h in oscillations is equally significant. For example, blocking HCN channels in the subthalamic nucleus alters the synchronization patterns of local field potentials, thereby influencing the synchronization of sleep spindles within the basal ganglia-cortical network [82]. Furthermore, I_h also mediates cross-frequency coupling. In hippocampal CA3 pyramidal neurons, increased I_h enhances theta power and shifts gamma amplitude to an earlier phase within the theta cycle, thereby enhancing theta-gamma phase-amplitude coupling, a mechanism implicated in memory encoding [81].

4. Region-Specific Dysfunction of HCN Channels in Depression and Anxiety

The expression and function of HCN channels in the CNS exhibit significant regional and subtype specificity [42]. This section synthesizes evidence from pathological models and intervention studies to clarify the complex contributions of different HCN channels subtypes across brain regions to depression- and anxiety-like behaviors (Table 2, Ref. [12,13,14,15,16,17,20,21,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99]).

4.1 Hippocampus

The hippocampus is a key structure involved in learning, memory, and emotional integration, and primarily expresses the HCN1 and HCN4 subtypes [38,39]. In the dorsal CA1 region, upregulation of HCN1 has been observed in multiple models, including stress, cerebral ischaemia, and neuropathic pain. This upregulation is observed to be associated with anxiety-like symptoms, evidenced by reduced exploration in the elevated plus maze (EPM) and open field test (OFT), and depression-like symptoms, evidenced by reduced sucrose preference in the sucrose preference test (SPT) and increased immobility time in the forced swim test (FST) [13,14,15,16,17]. It has been demonstrated that the knockdown of HCN1 in the dorsal CA1 region of the hippocampus produces anxiolytic and antidepressant effects [20,83]. Conversely, HCN4 knockdown in the dorsal hippocampus is associated with anxiety-like behavior, as reflected in reduced open-arm time in the elevated zero maze (EZM) test, suggesting that different subtypes may play opposing roles in emotional regulation [84]. Furthermore, in a model of perioperative neurocognitive disorder, downregulation of HCN2 is also linked to anxiety-like behavior [85], highlighting the functional complexity of HCN subtypes. Notably, most studies to date have focused on the dorsal hippocampus, which is preferentially involved in learning and spatial memory, whereas the ventral hippocampus is more directly connected to anxiety-related circuits such as the basolateral amygdala (BLA) and hypothalamus [100,101]. Whether HCN subtypes in the ventral hippocampus show similar or distinct patterns in emotional regulation warrants further investigation.

Table 2. Alterations of HCN channels in depression and anxiety.

Brain region	Subregion/neuron	HCN dysfunctions	Behavioral phenotypes	Models/interventions
Hippocampus	dCA1, DG	HCN1 expression↑, I_h↑	Depression↑, anxiety↑	CSDS [15,16], CUS [20,21], MCAO [13], SPS [14], ethanol withdrawal [17]
	dCA1	HCN1 expression↓, I_h↓	Depression↓, anxiety↓	HCN1 shRNA knockdown [83]
	Whole region	HCN2 expression↓	Anxiety↑	PND [85], GA [86]
	dCA1, CA3, DG	HCN4 expression↓	Anxiety↑	HCN4 shRNA knockdown [84]
PFC	Whole region	HCN1 expression↑	Depression↑, anxiety↑	SPS&S [87,88], PAE [89], SPS [90]
	mPFC	HCN1 expression↑	Anxiety↑	A/S [91]
VTA	Dopaminergic neurons	HCN2 I_h↑	Depression↑	CSDS [92]
		HCN2 I_h↓	Depression↑, anxiety↑	CMS [93]
		Impaired anchoring of HCN2/3 to GBR complexes	Anxiety↑	KCTD16-/- [94]
BLA	Pyramidal neurons	HCN1 expression↓, I_h↓	Anxiety↓	HCN1 shRNA knockdown [12]
			Anxiety↑	Tmem74-/- [95]
NAc	NAc shell ChIs	HCN2 expression↓, I_h↓	Depression↑	CSDS [96]
LHb	Whole region	HCN1 expression↑	Anxiety↑	morphine abstinence [97]
		HCN2 expression↑, I_h↑	Depression↑, anxiety↑	SNI [98]
Thalamus	Whole region	HCN2 expression↓	Anxiety↑	GA [86]
		HCN1 and HCN2 expression↑	Depression↑, Anxiety↑	SNI [99]

Abbreviations: I_h, hyperpolarization-activated current; CSDS, chronic social defeat stress; CUS, chronic unpredictable stress; CMS, chronic mild unpredictable stress; MCAO, middle cerebral artery occlusion; SPS, single prolonged stress; DG, dentate gyrus; shRNA, short hairpin RNA; PND, perioperative neurocognitive disorder; GA, general anesthesia; PFC, prefrontal cortex; SPS&S, single prolonged stress and electric foot shock; PAE, prenatal alcohol exposure; mPFC, medial prefrontal cortex; A/S, anesthesia/surgery; VTA, ventral tegmental area; GBR, $GABA_B$ receptor; KCTD16, potassium channel tetramerization domain-containing protein 16; BLA, basolateral amygdala; Tmem74, transmembrane protein 74; NAc, nucleus accumbens; ChIs, cholinergic interneurons; LHb, lateral habenula; SNI, spared nerve injury. ↑, increase; ↓, decrease.

4.2 Prefrontal Cortex

In the prefrontal cortex (PFC), upregulation of HCN1 and the resulting increase in I_h appear to be associated with depressive and anxiety-like effects. In Post-Traumatic Stress Disorder (PTSD) models involving single prolonged stress and single prolonged stress combined with electric foot shock, and in the prenatal alcohol exposure model, HCN1 upregulation in the PFC is associated with anxiety-like behavior, manifested by decreased center time in the open field test (OFT) and reduced exploration time in the open arm of the elevated plus maze (EPM); as well as depression-like behavior, manifested as increased immobility time in the FST and tail suspension test (TST), and reduced sucrose preference in the SPT [87,88,89,90]. In the medial prefrontal cortex (mPFC), upregulation of HCN1 expression was also observed in the anesthesia/-surgery model, and this upregulation was associated with anxiety-like behavior characterized by reduced activity in the central region of the OFT and increased avoidance of the open arm of the EPM [91]. These studies consistently link HCN1 upregulation in the prefrontal cortex (PFC) with negative emotional states. However, the PFC is functionally heterogeneous, and the consequences of HCN1 upregulation may differ across its subregions. For instance, the prelimbic and infralimbic medial prefrontal subregions exert opposing effects on fear expression and anxiety-like behavior [102,103], and future studies should distinguish between them.

4.3 Ventral Tegmental Area

Dysfunction of HCN2 in the ventral tegmental area (VTA) exerts more complex effects on emotional and behavioral manifestations. Chronic mild unpredictable stress (CMS) induces downregulation of HCN2-mediated I_h, and this downregulation is associated with a depressive and anxiety-like phenotype [93]. It has also been shown that a decrease in I_h caused by disrupting the membrane localization of HCN2/3 in the $GABA_B$ receptors (GBRs) is as-

sociated with anxiety [94]. In contrast, in the chronic social defeat stress (CSDS) model, susceptible mice exhibit upregulation of HCN2-mediated I_h in the VTA dopamine neurons, which is associated with depression-like behavior [92]. These opposing I_h changes may reflect differences in both stress modality and the neuronal populations examined. CMS involves prolonged, 5-week unpredictable and primarily non-social stressors, whereas CSDS consists of repeated social defeat over 10 days [93]. These distinct challenges engage different neuroendocrine and circuit-level responses [104], which may differentially modulate HCN channels function [105]. Furthermore, the CMS study specifically targeted VTA dopamine neurons projecting to the lateral shell of the nucleus accumbens (NAc) [93], while the CSDS study examined a broader NAc-projecting population [92]. Given the functional heterogeneity of NAc subregions, it remains possible that the two studies sampled different VTA-NAc projection subpopulations, contributing to the divergent I_h changes. The electrophysiological mechanisms underlying these stress-specific changes are discussed in Section 5.1.

4.4 Basolateral Amygdala

The amygdala plays a crucial role in processing fear and anxiety [106]. Within the BLA, the role of HCN1 appears to differ from that in the hippocampus and PFC. A study has revealed that Tmem74 knockout leads to downregulation of HCN1 in BLA pyramidal neurons, which also exhibits an anxiety-like phenotype evidenced by reduced entry frequency and retention time in the open arms of the EPM and EZM, as well as reduced center zone entries and time spent in the center zone in the OFT [95]. However, another study shows that selective knockdown of HCN1 in the BLA is associated with an anti-anxiety effect and increases interaction time during the SIT [12]. Several factors may account for this discrepancy. First, the two manipulations may differ in the neuronal subpopulations targeted. The Tmem74 study employed a CaMKIIα promoter to selectively target BLA pyramidal neurons [95], whereas the HCN1-shRNA study used a Synapsin promoter, which may drive expression in both pyramidal neurons and interneurons [12]. Consequently, the anxiolytic phenotype observed in the latter may not only be attributed to pyramidal neuron HCN1 loss alone. Instead, it may also involve disinhibition via interneuron HCN1 suppression. Second, Tmem74 knockout is present from early embryonic development, while HCN1 knockdown is induced acutely in adulthood. Prolonged HCN1 loss during development may therefore engage compensatory adaptations absent in the acute setting [12,95]. Additionally, it remains possible that the genetic tools used may carry the risk of off-target effects. Direct comparison of these manipulations in the same experimental framework may be needed to resolve their divergent behavioral outcomes.

4.5 Other Brain Regions

In other regions, such as the lateral habenula (LHb), the upregulation of HCN1 during morphine withdrawal is primarily associated with anxiety-like behavior [97]. In the spared nerve injury model, upregulation of HCN2 is associated with depression- and anxiety-like phenotypes [98]. In comparison, CSDS induced downregulation of HCN2 in cholinergic interneurons in the NAc shell, and this downregulation was associated with depressive-like behavior [96]. In the thalamus, prenatal exposure to sevoflurane downregulates HCN2 expression, and this downregulation is accompanied by autism-like phenotypes and anxiety-like behavior in offspring, manifested as reduced exploratory behavior in the open field test [86]. However, the spared nerve injury led to upregulation of HCN2 in the thalamus, which is also associated with depression- and anxiety-like behaviors [99]. It can therefore be hypothesized that the function of HCN2 in the thalamus may exhibit subnuclear heterogeneity.

In summary, the region-specific findings reviewed above reveal several main patterns. HCN1 upregulation is the most commonly reported change in the brain, seen in the hippocampus, PFC, and LHb across multiple stress paradigms. However, HCN2 changes seem to be dependent on the specific stress paradigm. Relatively few studies have examined HCN3 and HCN4 in the context of depression and anxiety. These findings also demonstrate that HCN channels dysfunction is predominantly observed in the context of stress exposure. This raises the question of how stress translates into altered HCN function at the molecular level. A growing number of studies are pointing to the involvement of neurotoxic processes in depression, driven by persistent neuroinflammation, axonal injury, and disrupted calcium homeostasis [107,108]. Each of these factors may impact HCN channels through distinct mechanisms. Specifically, pro-inflammatory cytokines and oxidative stress can suppress channel activity through phosphorylation [109,110], axonal and microtubule damage may impair HCN trafficking to the dendritic membrane [111], and reduced serum calcium may further compromise channel gating [9]. Notably, HCN1 knockdown has been shown to alleviate depression-like behavior partly by suppressing the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome pathway [13], suggesting a bidirectional relationship between HCN channels function and neuroinflammation. These observations suggest the hypothesis that neurotoxic processes may be associated with HCN channels dysfunction in depression. Consequently, it may suggest the potential for a more comprehensive elucidation of the pathogenesis of depression. Accordingly, this hypothetical scenario also suggests that interventions that target neurotoxicity might exert antidepressant effects via the preservation of HCN channels function.

Table 3. I_h regulation of MPOs and neuronal excitability in relation to depression/anxiety phenotypes.

Brain region	Neurons	I_h alterations	Membrane and resonance properties	Neuronal excitability	Behavioral phenotypes
Dorsal hippocampal CA1	Pyramidal neurons	HCN1 I_h↑ [14,15,16,20,21]	R_{in}↓, f_R↑	Firing rate↓, AHP↑	Depression↑, anxiety↑
		HCN1 I_h↓ [83]	R_{in}↑, membrane τ↑, f_R↓	Firing rate↑	Depression↓, anxiety↓
mPFC PrL	L5 Pyramidal neurons	I_h↑ [112]	R_{in}↓, f_R↑	Firing rate↓, rheobase↑	Depression↑, anxiety↑
VTA	Dopaminergic neurons	I_h↑ [113] I_h activation at synapses ↓ [94]		Firing rate↑ Latency to firing↑, firing rate↓	Depression↑ Anxiety↑
	Dopaminergic neurons projecting to NAc	HCN2 I_h↑ [92]		Firing rate↑	Depression↑
	Dopaminergic neurons projecting to NAc lateral shell	HCN2 I_h↓ [93]		Firing rate↓	Depression↑, anxiety↑
NAc shell	ChIs	HCN2 I_h↓ [96]		Firing rate↓	Depression↑
BLA	Pyramidal neurons	HCN1 I_h↓ [12] HCN1 I_h↓ [95]	 R_{in}↑, membrane τ↑	Rheobase↑ Firing rate↑	Anxiety↓ Anxiety↑
LHb	Unspecified	HCN2 I_h↑ [98]	R_{in}↓	Threshold↓, firing rate↑	Depression↑, anxiety↑

Abbreviations: MPO, subthreshold membrane potential oscillation; R_{in}, input resistance; f_R, resonance frequency; AHP, afterhyperpolarization; τ, time constant; PrL, prelimbic cortex. ↑, increase; ↓, decrease.

5. Electrophysiological Mechanisms of HCN I_h Abnormalities in Depression and Anxiety

5.1 Abnormalities in MPOs and AP Firing

The influence of I_h on neuronal excitability, AP firing, and MPOs is modulated by its effect on the passive membrane properties and resonant characteristics of neurons. A series of pathological changes in these aspects constitutes the pivotal electrophysiological mechanism underlying the development of depression and anxiety. However, changes in I_h and the relevant electrophysiological effects vary across different brain regions and specific neuronal types (Table 3, Ref. [12,14,15,16,20,21,83,92,93,94,95,96,98,112,113]).

In CA1 pyramidal neurons of the dorsal hippocampus, the HCN1-mediated increase in I_h under stress conditions generally leads to alterations in MPO traits and a reduction in AP firing, which are thought to impair hippocampal memory and are associated with depression- and anxiety-like behaviors [14,15,20,21]. For example, in mice susceptible to CSDS, HCN1 expression is upregulated in dorsal CA1 neurons, and the increased I_h leads to a reduction in the R_{in}, producing a shunting effect that affects dendritic integration and the ability to drive membrane depolarization, ultimately reducing neuronal excitability, and this reduction is associated with anxiety-like behavior [15]. In the chronic unpredictable stress (CUS) model, an increase in the I_h is followed by a rise in the f_R and a decrease in action potential firing rate, indicating reduced intrinsic neuronal excitability, which has been found to correlate with depressive and anxiety phenotypes [20,21]. These studies may point to enhanced HCN1-mediated I_h function as a key electrophysiological marker of emotional dysfunction in the hippocampus. Kim et al. [83] decreased the I_h by knocking down HCN1, observing an increase in the number of APs and a greater summation of afferent excitatory postsynaptic potentials, which increases neuronal excitability and produces antidepressant and anxiolytic effects.

In the PFC, the absence of histamine H_2 receptors in glutamatergic neurons can enhance I_h, reduce the AP firing rate, and consequently induce phenotypes of social withdrawal and anhedonia. Furthermore, the study confirmed that HCN channels dysfunction is a key mechanism underlying the reduced excitability of mPFC glutamatergic neurons, and this effect can be reversed by H_2 receptor agonists [114,115,116]. In line with this, a recent study reveals that neonatal maternal separation leads to an increased I_h in L5 pyramidal neurons of the prelimbic region (PrL), resulting in a decrease in R_{in} and a shift of f_R toward higher frequencies, and a reduction in the intrinsic excitability of pyramidal neurons, which is associated with a phenotype of depression and anxiety [112].

In dopamine neurons of the VTA, HCN2-mediated I_h changes differ between CMS and CSDS, as described in Section 4.3. Under CSDS, elevated I_h in susceptible mice enhances both tonic and burst firing [113]. Notably, resilient mice show an even larger I_h increase. However, this increase is balanced by a compensatory upregulation of potassium currents, which keeps net excitability within a normal range [92]. Thus, homeostatic compensation is also engaged in shaping the behavioral manifestation of altered I_h. In the CMS model, by contrast, I_h is reduced and firing frequency decreases [93]. Furthermore, KCTD16-dependent anchoring of HCN2 and HCN3 to the GBR provides an additional layer of regulation, as disrupting this complex prolongs the inhibition of dopaminergic neuron firing [94]. Together, these findings point to a model in which the net impact of I_h changes on VTA neuron output depends on a combination of factors, including the nature of the stress, the projection target of the neurons involved, and the concurrent adaptation of other ion conductances.

In BLA pyramidal neurons, reduced I_h is accompanied by increased AP frequency and an anxiety phenotype, as observed following Tmem74-mediated uncoupling of HCN1 [95]. In contrast, neuropeptide Y (NPY)-induced HCN1 downregulation reduces I_h and decreases neuronal excitability, an effect associated with an anti-anxiety phenotype [12]. Additionally, Jia Cheng and colleagues found that downregulation of HCN2 in cholinergic interneurons in the NAc shell led to a reduction in I_h, resulting in a decrease in tonic firing rate, which is associated with a depressive phenotype [96].

Studies in the LHb have shown that enhanced I_h driven by HCN1 or HCN2 upregulation increases neuronal excitability and drives burst firing, which leads to dysfunction in neurotransmitter systems (*e.g.*, dopamine and serotonin) by enhancing inhibitory output to downstream reward-related brain regions (*e.g.*, the VTA and dorsal raphe nucleus) [97,98].

Collectively, in the pathophysiology of depression and anxiety, elevated HCN1 I_h is accompanied by reduced excitability in the hippocampus and PFC [14,15,16,20,21,112], whereas in the VTA and LHb, HCN2 I_h changes are positively coupled with excitability [93,98]. In the BLA, reduced HCN1 I_h is associated with enhanced excitability [95], although a conflicting finding exists in which HCN1 I_h reduction produces the opposite excitability change and an anxiolytic effect [12], as discussed in Section 4.4. This regional heterogeneity reinforces the principle that therapeutic strategies targeting HCN channels must be tailored to the specific brain region and the pathological direction of I_h change.

5.2 Abnormalities in Network Oscillations and Neuronal Synchrony

Although previous studies have described a direct link between HCN I_h dysfunction and alterations in network oscillations at specific frequency bands, the complete causal chain linking these oscillatory abnormalities to depression and anxiety remains to be elucidated. This section summarizes the effects of HCN I_h abnormalities in brain regions associated with depression and anxiety on network oscillations, and proposes reasonable hypotheses regarding their links to emotional and behavioral phenotypes (Table 4, Ref. [117,118,119,120,121]).

In the hippocampus, alterations in the HCN I_h are closely associated with abnormalities in theta rhythms. In mice with chronic temporal lobe epilepsy, the amplitude of the I_h in the dendrites of hippocampus CA1 pyramidal neurons is significantly reduced, and the activation curve shifts to the left, resulting in a decrease in the f_R of theta oscillation and impaired phase response capability [117]. Moreover, HCN channels in GABAergic neurons within the medial septum–diagonal band (MSDB) serve as a key pacemaker for the generation of hippocampal theta rhythms, blocking this current results in a significant reduction in theta power [118,119]. This evidence suggests that downregulation of HCN I_h function may be associated with a reduction in hippocampal theta oscillations. However, studies on anxiety indicate that enhanced theta synchrony between the ventral hippocampus and the BLA [122,123] and between the ventral hippocampus and the mPFC [124,125,126] is a hallmark of a state of anxiety. As numerous studies have shown that upregulation of HCN expression and increased I_h in the hippocampus is associated with anxiety-like behavior [13,14,15,20,21], it can be hypothesized that functional upregulation of HCN I_h may be associated with enhanced hippocampal theta oscillations, thereby promoting anxiety. Specifically, upregulation of I_h in CA1 pyramidal neurons of the dorsal hippocampus increases f_R, accompanied by anxiety-like behavior [20,21]. Based on these findings, one may hypothesize a possible association between I_h upregulation and enhancing sensitivity of hippocampal pyramidal neurons to theta-band input and promoting synchronized subthreshold theta oscillation within the hippocampus. Although such oscillations may coincide with a decrease in total AP number, the temporal precision of output could be enhanced, which may in turn facilitate theta-frequency synchronization with the BLA and mPFC and contribute to excessive synchronization within anxiety-related emotional networks. It must be emphasized that this proposed cascade has not been directly demonstrated experimentally. It is evident that further research is required to test this hypothesis.

In the PFC, inhibition of HCN1-mediated I_h by type I interferons significantly shifted f_R of pyramidal neurons in layer 5 of the cortex and increased peak impedance, causing the neurons to respond more preferentially to low-frequency inputs [120]. This shift toward lower frequencies is consistent with oscillatory patterns observed in depressive animal models, such as the increased low-frequency oscillation power in the mPFC of CSDS-susceptible mice

Table 4. Effects of HCN dysfunction on network oscillations.

Brain region	HCN dysfunction	Network oscillation abnormalities
Hippocampus	CA1 pyramidal neurons (distal dendrites), I_h↓	Hippocampal theta power and peak frequency reduced [117]
	MSDB GABAergic neurons, I_h↓	Hippocampal theta power reduced, auditory stimulus-induced theta bursts abolished [118]
		Hippocampal theta peak frequency decreased from 8–10 Hz to 6–8 Hz [119]
Neocortex	Layer 5 pyramidal neurons, HCN1 I_h↓	The power of higher frequencies in the neocortex reduced [120]
Global brain	Global HCN1 KO	Cortical power broadly decreased in the 3–20 Hz range, with significant reductions in the theta and alpha bands [121]

Abbreviations: MSDB, medial septum-diagonal band of Broca; GABA, gamma-aminobutyric acid; KO, knockout. ↑, increase; ↓, decrease.

[127], raising the possibility that I_h inhibition may enhance low-frequency oscillatory responses under stress. Furthermore, global HCN1 knockout in mice reduces cortical power in the theta and alpha bands [121]. While this study did not assess affective behaviors, alterations in theta and alpha activity are frequently observed in psychiatric populations. For instance, Patients with temporal lobe epilepsy and comorbid depression exhibit significantly reduced PFC theta oscillations and functional connectivity when performing cognitive tasks [128]. At the same time, individuals with MDD exhibit abnormally enhanced functional connectivity in the alpha band, such as increased cross-regional alpha connectivity between the ventromedial prefrontal cortex and the left dorsolateral prefrontal cortex [129,130,131]. These observations suggest that HCN I_h dysfunction may influence the generation of oscillations and functional connectivity in the theta/alpha bands, with potential consequences for executive control over emotions and cognition in the PFC. However, the causal chain from HCN1 dysfunction to theta/alpha alterations to depression-related cognitive impairment has not been experimentally demonstrated and remains a hypothesis requiring further investigation.

6. Therapeutic Implications of Targeting HCN Channels

6.1 Targeting Strategies Across Brain Regions

As discussed in Section 4, studies have revealed differences in the expression and function of HCN channels across different brain regions, as well as the complex changes in pathological states of depression and anxiety. These findings suggest that precision therapeutic strategies targeting HCN channels must be based on specific brain regions, neuronal types, and HCN subtypes. A growing body of evidence from interventional studies shows that modulating the function of specific HCN subtypes in particular brain regions can effectively reverse depression- and anxiety-like behaviors through different molecular mechanisms.

A wealth of evidence indicates that inhibiting HCN1 channels in the hippocampus may be a core strategy for producing anti-anxiety and antidepressant effects [15,20,21]. As described in Section 4.1, stress upregulates HCN1 expression and I_h in dorsal CA1 pyramidal neurons. Targeted knockdown of HCN1 in this region via lentiviral shRNA reverses stress-induced electrophysiological abnormalities, restores neuronal excitability, and exerts antidepressant and anti-anxiety effects [83]. In the dentate gyrus, HCN1 knockdown in a post-stroke depression model alleviates social avoidance and anhedonia by suppressing the NLRP3 inflammasome pathway [13].

In the PFC, targeting the HCN1 channel has also demonstrated therapeutic potential. In rats with a PTSD model, HCN1 expression is upregulated in the PFC, accompanied by downregulation of BDNF and postsynaptic density protein [87,88]. Intracerebral injection of the HCN channels antagonist ZD7288 downregulates HCN1 expression, restores the BDNF-mTOR signaling pathway, and improves synaptic transmission, thereby alleviating behavioral despair [87]. It is worth noting that ketamine, a clinically effective drug, may restore BDNF levels and repair synaptic ultrastructure by downregulating the overexpression of HCN1 in the PFC, which is associated with improving depression- and anxiety-like behaviors [88,90]. As an effective inhibitor of the HCN1 channel, ketamine inhibits I_h in cortical neurons, leading to membrane hyperpolarization and enhanced dendritic-somatic synaptic coupling. These effects are thought to contribute to cortical synchronization and slow rhythmic activity [132].

Targeted strategies in the VTA should focus on the HCN2 subtype. In the CSDS model, where VTA dopamine neurons are hyperactive [92,113], the direct microinjection of an HCN channels blocker into the VTA rapidly exerts an antidepressant effect by restoring normal I_h current and neuronal firing activity [113,133,134]. Conversely, in the CMS model, where HCN2 function is downregulated, overexpression of HCN2 prior to stress prevents the development of anhedonia and behavioral despair [93]. These findings may suggest that interventions targeting HCN2 in the VTA should aim to restore abnormal firing patterns to a physiological equilibrium.

Intervention studies in the BLA and the LHb have further confirmed the critical role of HCN channels in emotional circuits. In the BLA, repeated NPY injections down-

regulate HCN1 expression and I_h, producing sustained anti-anxiety and stress-resilience effects that are fully recapitulated by lentiviral shRNA-mediated HCN1 knockdown [12]. In the LHb, both injection of ZD7288 and knockdown of HCN1 and HCN2 effectively reverse anxiety- and depression-like behaviors [97,98].

The above studies suggest that HCN subtypes targeting specific brain regions hold clear therapeutic potential, the key to which lies in restoring the balance of neuronal excitability under pathological conditions, rather than simply inhibiting or activating channel function. Future research needs to elucidate the dynamic functional changes of HCN channels across different stress models and disease stages, in order to develop more precise intervention strategies.

6.2 Challenges and Future Directions for Clinical Translation

6.2.1 Preclinical Evidence

Although HCN channels show great promise in the treatment of depression and anxiety, translating this into clinical practice remains challenging. It must be emphasized that no HCN channel-directed drug has received regulatory approval for the treatment of depression or anxiety disorders. All findings discussed in this section are derived from preclinical studies, and substantial additional work is required before clinical translation can be considered.

Currently, ivabradine is the only HCN channels blocker in clinical use, which primarily slows the heart rate by inhibiting cardiac HCN channels [135,136]. Preclinical studies have shown that ivabradine alleviates anxiety-like behavior in mice [137]. However, its unavoidable side effect of bradycardia limits its use in the treatment of depression and anxiety. A recent cryo-EM study has resolved the mechanism by which ivabradine binds to the HCN1 channel, revealing that it acts on a novel pocket formed by the S4, S1, and HCN domains. Through structure-based virtual screening, the researchers further found that haloperidol, a drug with brain permeability, is able to bind to the same pocket and inhibit the HCN1 channel [138]. Furthermore, recent research has successfully identified the RO series of highly selective HCN1 inhibitors capable of penetrating the blood-brain barrier, most notably represented by RO-275, which exhibits submicromolar potency against HCN1, with unprecedented selectivity over HCN2, HCN3, and HCN4, and has been shown to improve cognitive function *in vivo* without affecting heart rate [139].

Beyond direct channel blockade, targeting the HCN auxiliary subunit, tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b), represents an alternative strategy. TRIP8b is specifically expressed in the brain alongside HCN channels [140,141], and disrupting the TRIP8b-HCN interaction reduces dendritic HCN membrane localization and produces antidepressant-like effects in mice [142]. More importantly, different subtypes of TRIP8b vary in their distribution and expression levels across brain regions, and their regulatory effects on different subtypes of HCN channels may also differ significantly [143], which suggests that small-molecule inhibitors targeting the interaction between specific TRIP8b subtypes and HCN channels subtypes hold potential for the precise regulation of HCN function in specific brain regions.

6.2.2 Clinical Challenges

Despite the preclinical promise outlined above, several significant challenges must be addressed before HCN-targeted therapies can be translated to the clinic. A central challenge for HCN-targeted drug development is achieving meaningful selectivity. The discovery of selective modulators for the HCN subtype could potentially be achieved through drug screening using recombinant systems. However, the subtype selectivity observed in recombinant systems must be validated in native tissues, as native HCN channels are predominantly heteromeric, most commonly HCN1/HCN2 and HCN2/HCN4, and these heteromers exhibit biophysical properties distinct from their homomeric counterparts [144,145]. Compounds showing selectivity for a given subtype in recombinant assays may therefore exhibit altered efficacy when acting on native heteromeric complexes. Moreover, pathological states can alter HCN subunit expression ratios and thereby shift the probability of heteromeric assembly. Developmental seizures have been shown to alter HCN subunit expression ratios and promote HCN1/HCN2 heteromeric assembly, leading to persistent changes in I_h that contribute to epileptogenesis [146]. Whether similar disease-driven changes in heteromer composition occur in depression and anxiety is unknown, but if heteromer configuration shifts with disease progression, the pharmacological target may become a moving entity, increasing the risk of reduced efficacy or off-target effects.

Even if highly selective compounds are obtained, the challenge of delivering them precisely to the target brain regions remains a key hurdle to clinical translation. Nanoparticle-based targeted drug delivery technology that has emerged in recent years offers a new approach to this, utilizing functionalized nanocarriers such as liposomes conjugated with brain-specific ligands [147,148] or polymeric nanoparticles [23,149] loaded with HCN subtype-selective modulators, which may enable the drug to cross the blood-brain barrier and accumulate specifically in the brain. On this basis, focused ultrasound technology has further facilitated the delivery process. On the one hand, focused ultrasound can transiently and reversibly open the blood-brain barrier [150]; on the other hand, it can release the carried drugs through mechanisms such as acoustic droplet vaporization and thermal bioswitches [151], offering promising strategies for achieving brain-specific drug accumulation, though these technologies have yet to be applied to HCN-targeted interventions in depression/anxiety models.

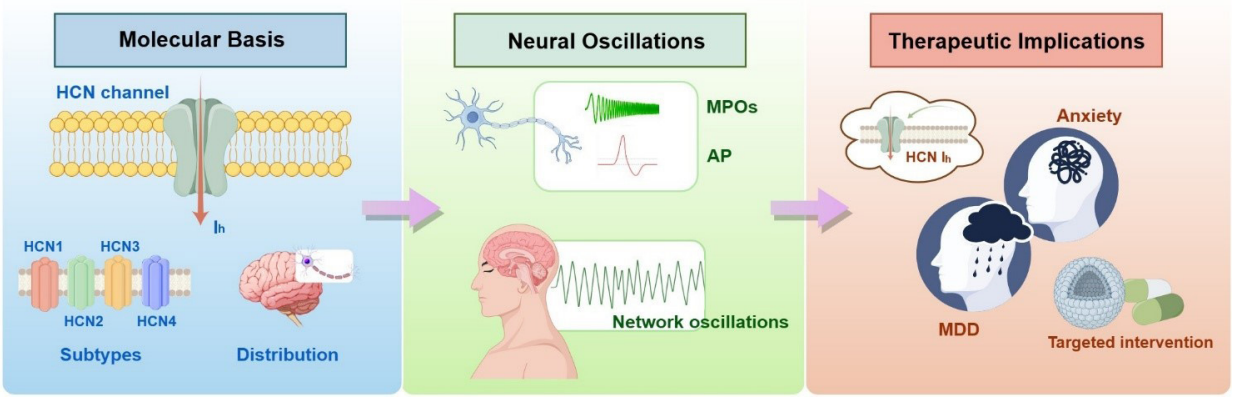


Fig. 3. Mechanisms and precision therapy of HCN channels in depression and anxiety. MPOs, subthreshold membrane potential oscillations; AP, action potential; MDD, major depressive disorder.

A further direction involves non-invasive neuromodulation. Temporal interference (TI) stimulation, as an emerging non-invasive technique for stimulating deep brain structures [152], has been preliminarily shown to alleviate symptoms of depression and cognitive impairment [153]. Current hypotheses suggest that TI stimulation may modulate MPOs in neurons within deep brain regions to achieve therapeutic effects by utilizing high-frequency external electric fields [154,155]. Therefore, elucidating how I_h relates to network oscillations may help optimize TI stimulation protocols and inform the development of other neuromodulation strategies targeting this pathway.

7. Conclusions and Future Perspectives

Current evidence strongly suggests that HCN I_h plays a significant role in the pathophysiological mechanisms of depression and anxiety (Fig. 3). This review systematically examines the differences in the expression and function of HCN channels across various emotion-related brain regions, revealing the region- and subtype-specific nature of their regulatory effects. Under physiological conditions, I_h contributes to the generation of MPOs by modulating neuronal resonance properties, subsequently influencing the rhythm and synchrony of network oscillations. Under pathological conditions, abnormalities in I_h function can disrupt both cellular-level electrophysiological activity and inter-regional network coordination, potentially constituting a key mechanism underlying depression and anxiety.

The central advantage of HCN channel-targeted therapy lies in its precise correspondence between brain regions and subtypes. As outlined in this review, the effects of the same subtype on emotional regulation may vary across different brain regions. Consequently, accurately identifying the HCN subtypes undergoing pathological changes in specific brain regions and targeting them for intervention is crucial to ensuring therapeutic efficacy. Accordingly, the translational roadmap for HCN-targeted therapy begins with brain region- and subtype-resolved preclinical studies to define the precise cellular and circuit mechanisms underlying depression and anxiety. These insights can enable the rational design of brain-penetrant, subtype-selective modulators, optimally combined with circuit-specific delivery systems to maximize efficacy while avoiding cardiac and off-target effects. Before clinical testing, neurophysiological biomarkers should be established to quantify target engagement and guide patient stratification. Following this staged progression from mechanism to molecule, delivery, and biomarker-guided trials, HCN channels modulation can advance systematically toward precision treatments for mood disorders.

A significant limitation of this review, which must be acknowledged, is the underrepresentation of sex as a biological variable. Although the majority of preclinical studies reviewed here were conducted exclusively in male animals, evidence indicates that estrogen can upregulate HCN1 and HCN2 transcription [156] and modulate I_h in an estrous cycle-dependent manner [157]. Thus, the efficacy of HCN-targeted interventions may vary depending on sex and hormonal background. This endocrine tuning of HCN function provides a plausible cellular substrate linking the well-documented sex differences in depression and anxiety prevalence to HCN channels dysfunction, and argues for the explicit inclusion of sex as a biological variable in future HCN-focused mood disorder research.

Future studies should integrate brain-region-specific gene editing, *in vivo* multichannel recording, and optogenetics to define HCN subtype functions across circuits and establish causal links between I_h-driven network activity and emotional phenotypes, thereby advancing precision therapies for depression and anxiety.

Author Contributions

CLL: Data curation, Investigation, Methodology, Validation, Visualization, and Writing – original draft. MQL: Funding acquisition, Methodology, Project administration, Resources, Supervision, and Writing – original draft. CL:

Validation, Writing – review & editing. WGX: Visualization, Writing – review & editing. XW: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, and Writing – review & editing. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank Figdraw for assistance in creating the figure.

Funding

This work was supported by the Natural Science Foundation of Jiangxi Province (Grant No. 20242BAB25480), the National Natural Science Foundation of China (Grant No. 82360278), and the Science and Technology Program of Jiangxi Provincial Health Commission (Grant No. 202510036).

Conflicts of Interest

The authors declare no conflicts of interest.

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