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Opinion

Alzheimer's Disease, Piezo2 Channelopathy, Piezo1 Channelopathy, and the Body-Wide Piezo2 System

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Abstract

Alzheimer's disease initiates pathophysiology in the 10 to 20 years prior to detectable clinical symptoms. A recent genetic analysis implicated the critical role of Piezo2 in Alzheimer's disease pathophysiology. A recent genetic study, involving PIEZO1 manipulation, showed that phosphatidylinositol 4,5-bisphosphate (PIP_2) rectified brain capillary endothelial Piezo1 channelopathy in a mouse model of Alzheimer's disease. However, the present opinion paper posits that the initiating microdamage is in the prefrontal cortex, further upstream of pathophysiology, namely an irreversible Piezo2 channelopathy of glutamatergic terminals that is proposed to finely regulate oxytocin release resulting from stressful ultradian events, leading to impaired ultradian rhythm. The involvement of Piezo2 in the defensive arousal response reveals an underlying body-wide Piezo2 system of which the proposed prefrontal Piezo2 channelopathy is possibly a critical locus. PIP_2 is emerging as a potential treatment method for Piezo channelopathy in Alzheimer's disease. However, the challenge of its more precise administration to target affected regions of the brain still remains.

Keywords: Alzheimer disease; channelopathy; oxytocin; Piezo1; Piezo2; ultradian rhythm

1. Introduction

A variant of PIEZO2 was recently shown to be protective against Alzheimer's disease (AD) in the Hispanic population [1]. This important analysis implicated the potentially critical role of Piezo2 in AD pathophysiology. Another recent study mimicked acquired Piezo1 channelopathy by point mutation manipulation on PIEZO1 [2]. That study also showed that phosphatidylinositol 4,5-bisphosphate (PIP_2) administration ameliorated brain capillary endothelial Piezo1 channelopathy in a mouse model of AD [2].

It is noteworthy that inherited variants of PIEZO1 and PIEZO2 have been recognized in certain diseases. The "not inherited" type of Piezo channelopathy, namely acquired Piezo2 channelopathy and its mechanism was first proposed in 2021 [3,4]. Two years later, a study confirmed the existence of acquired Piezo2 channelopathy in a neurogenetic disease called Angelman Syndrome, without known pathogenic Piezo2 variants [5], and reconfirmed it again in 2025 [6]. In parallel, two genetic analyses, one in 2023 and one in 2025, on an amyotrophic lateral sclerosis (ALS) cohort indirectly also verified its existence [7]. In addition, the critical mechanistic role of PIP_2 in the development of acquired Piezo2 channelopathy was first put forward in relation to ALS in 2022 [4]. Moreover, this crucial role of PIP_2 was even implicated in the potential treatment of acquired Piezo2 channelopathy by diclofenac in 2022 [8].

2. Acquired Piezo2 Channelopathy

The initiating pathophysiology of ALS is hypothesized to be an irreversible acquired Piezo2 channelopathy, with underlying genetic and environmental risk factors or, equivalently, an irreversible proton affinity switch in proprioceptive glutamatergic nerve terminals [4]. Proprioceptive miswiring may develop as a result of this irreversible Piezo2 microdamage that terminally impairs the Piezo2-initiated ultradian ultrafast muscle spindle–hippocampal axis in ALS [9]. In contrast, the irreversible Piezo2 channelopathy-induced impairment of the glutamatergic terminal Piezo2-initiated ultradian ultrafast prefrontal–hippocampal axis has been proposed to initiate the disease pathophysiology in AD [9] in the presence of genetic and environmental risk factors. Accordingly, disconnection of the vesicular glutamate transporter Vglut1 and Vglut2 (glutamate/proton antiports) has been suspected to occur in the acute, chronic, and irreversible form of acquired Piezo2 channelopathy [4]. However, irreversible Piezo2 channelopathy may even reduce the expression of Vglut1 and Vglut2, as has been observed in the prefrontal cortex of AD patients [10]. Piezo2-initiated ultradian ultrafast brain axes have been proposed to be temporarily synchronized to ultradian brain rhythms with the hippocampal theta rhythm and medulla firing via long-distance synchronous Piezo2-Piezo2 crosstalk through Vglut2 in a heart-rate-dependent fashion [7], constructing the base of

an underlying body-wide Piezo2 system that was initially proposed in 2022 [4].

3. Piezo2 and the Defensive Arousal Response

In support, a traumatic brain injury (TBI) study showed that the body-wide Piezo2 system is indeed operational, as reflected in the defensive arousal response (DAR). The DAR is a critical survival mechanism that is associated with motor abilities, and is called forth when an unpredictable threat is perceived by visual and auditory cues. The most significant finding of that study was that chemogenetic activation of trigeminal Piezo2 restored motor abilities and visual DAR in TBI mice [11]. Notably, TBI, especially repeated TBI, is a significant risk factor for AD development. Furthermore, the cingulate cortex (CC), a goal-oriented cognitive planning region of the prefrontal cortex, is a critical locus for (ultra)fast decision-making and response of DAR during arousal-associated threat appraisal. The interplay of cognitive control, emotional reactivity, and autonomic response results in the decision/response initiation of either the "fight-or-flight" or the freeze response, during this threat-appraisal. Another important consideration is the bidirectional Vglut2-containing glutamatergic projections of the CC to the eye, ear, thalamus, and hypothalamus, in addition to the hippocampus. Large-fiber glutamatergic afferents projecting from the CC to the thalamus may be particularly important when it comes to "fight-or-flight" or freeze appraisal. Indeed, there are cortical glutamatergic afferents from the medial prefrontal cortex that preferentially innervate the converging and segregating excitatory glutamatergic and inhibitory GABAergic calretinin-positive core of the paraventricular thalamic nucleus, which serves as a "critical bottleneck in the subcortex—cortex communication" [12]. This calretinin-positive thalamic core may be involved in the conscious "fight-or-flight" or freeze appraisal during arousal to the CC through the 'decision-making' medial prefrontal cortex. This "fight-or-flight" or freeze appraisal and decision-making process may present a critical initiating step prior to DAR onset. This is especially true if we consider that hippocampal theta-wave activation precedes the onset of moderate or more intense exercise [13]. Therefore, hippocampal theta might be on during the "fight-or-flight" appraisal/decision-making process already, leading to moderate or more intense exercise.

I suggest that emotional reactivity is modulated by the abovementioned Vglut2-containing, large fiber, glutamatergic afferents to the paraventricular nuclei of the hypothalamus from the CC as well, namely coupling heartbeat pulsatility through the pressure-pulse-detecting capability of Piezo2. This would lead to increased oxytocin release based on their terminal efferent function. The proposed target cells are the Piezo2-containing oxytocinergic cells in the paraventricular hypothalamic nuclei [14]. The oxytocin-release-associated pathway is not only important for social-behavior modulation, neuroinflammation, and pain suppression, but also for arousal. Note that stress-related neurodegenerative microdamage-induced loss of fine/ultrafast modulation of oxytocin release along this pathway has been associated with findings that showed that oxytocin administration is neuroprotective and restores both social and non-social memory in an AD model [15]. Moreover, it is evident that the CC is an early target of AD pathology [16]. Consequently, I suggest that the age-dependent protein-degradation-derived Piezo2 channelopathy of the Piezo2 content with the paraventricular hypothalamic nuclei induces Vglut2 disconnection in the CC, which in turn impairs glutamatergic coupling between the CC and hippocampal theta rhythm. Moreover, this degenerative trajectory, leading to irreversible Piezo2 channelopathy and resultant Vglut2 disconnection along this pathway, may be the reason why alterations in hippocampal oscillations and theta-gamma coupling were evident prior to Aβ overproduction in a mouse model of AD [17]. It is noteworthy that AD-associated hypersynchrony of hippocampal theta has been linked to altered glucose metabolism [18], which the author suggests is a consequence of irreversible Piezo2 channelopathy-induced proton reversal and resultant oxidative phosphorylation (OXPHOS) depletion [4,19]. In support, the CC exhibited the earliest and largest reduction in brain energy metabolism in AD patients [20].

4. Piezo2 Channelopathy-Induced Metabolic and Energy Generation Switch

The aforementioned metabolic- and energy-generation switch induced by acquired Piezo2 channelopathy may also come with lipid dysregulation. Accordingly, acquired Piezo2 channelopathy may dissociate auxiliary proteins, such as TMEM120A/TACAN from Piezo2 due to excessively prolonged excitation under allostatic stress. Depletion of negatively charged lipids, including cholesterol and PIP_2, due to prolonged Piezo activation, may contribute to charge alteration within the electrostatic microenvironment, eventually leading to a proton-affinity switch and proton reversal [19]. Of note, the role of apolipoprotein E4 (APOE4) should be considered in this process as well when it comes to AD. However, it is not the subject of this opinion paper. Resultant TACAN dissociation from Piezo2 may activate phospholipase D, which in turn activates lipoxygenase. As an analogy, it has been previously proposed that phospholipase C activates lipoxygenase, thereby contributing to Piezo1 channelopathy. This analogy may be extended as Piezo2-Piezo1 crosstalk has been suspected in a given compartmental microenvironment under homeostatic conditions, and Piezo channelopathy impairs this bidirectional crosstalk [4]. It is also noteworthy that dysregulated phospholipase C signaling is part of AD pathophysiology [2], which is presumed to be the result of Piezo1 channelopathy. However, the proposed upstream initiating mechanism is the suggested

irreversible Piezo2 channelopathy in the prefrontal cortex on glutamatergic terminals in AD [9]. Hence, the aforementioned mimicked brain capillary endothelial-acquired Piezo1 channelopathy in AD [2] has been suggested to be a direct consequence of impaired Piezo2-Piezo1 crosstalk resulting from irreversible Piezo2 channelopathy, leading to neurovascular decoupling. Therefore, the brain capillary endothelial Piezo1 channelopathy is merely a downstream consequence of the proposed initiating pathology. In other words, a body-wide Piezo2 system is operational within an even broader body-wide Piezo system that is interconnected through compartmental crosstalk between Piezo2 and Piezo1, affecting the co-functioning compartments and the whole body. Consequently, brain capillary endothelial Piezo1 channelopathy may reflect an underlying Piezo2 channelopathy within the same compartment or within functionally interconnected compartments [4].

The effect of this acquired Piezo2 channelopathy on glutamatergic terminals, induced by excessively prolonged excitation under allostatic stress, may impair the quantum-mechanical free-energy stimulation aspect of Piezo2-initiated, non-synaptic, ultrafast, synchronous proton signaling through Vglut2 [19]. This non-synaptic signaling mechanism underpins the proposed ultradian ultrafast brain axes, such as those proposed in AD and ALS [9]. Correspondingly, accumulation of extracellular protons leading to a proton affinity switch may increase the risk, during prolonged excitation under allostatic stress, of the aforementioned miswiring towards activated lipoxygenase-induced proton-coupled electron transfer and concerted proton tunneling–electron tunneling [19]. In support, diclofenac attenuates excitation through cyclooxygenase inhibition, but its lipoxygenase-blocking activity may also prevent proton miswiring. This may explain why diclofenac effectively prevented forced-lengthening-induced delayed-onset muscle soreness, a process considered analogous to prolonged excitation under allostatic stress [19], and may reduce AD risk [21].

Administering negatively charged PIP_2 could ameliorate Piezo channelopathy by rectifying the electrostatic microenvironment and restoring previously unrecognized ultrafast proton signaling, because the positively charged arginine substitution introduced by the point mutation of PIEZO1 at a critical site [2] appears to be detrimental without such correction. Furthermore, PIP_2 is also a nuclear RNA-dependent spatiotemporal orchestrator through electrostatic interactions [22]. Since Piezo2 channelopathy was suggested to be a principal transcription activator [4,19], Piezo-channelopathy-associated PIP_2 depletion or, more specifically, its nuclear translocation, may contribute essentially to transcription activation due to proton reversal. However, the impaired ultradian prefrontal–hippocampal axis resulting from irreversible Piezo2 channelopathy in prefrontal glutamatergic terminals may not only chronically dysregulate this transcription activation, but may also be a major contributor to hippocampal theta-rhythm-related cognitive impairment, dysfunctional adult hippocampal neurogenesis, dysregulated systemic inflammation, and impairment of long-term spatial memory in AD [9].

Finally, one cardinal symptom of acquired Piezo2 channelopathy is insulin resistance [9,19], as alterations in glucose metabolism and brain insulin resistance are evident in AD. In support, oxytocin has an immediate positive modulatory effect on insulin sensitivity [23]. Therefore, the irreversible-Piezo2-channelopathy-induced loss of fine control over oxytocin release from the paraventricular hypothalamic nuclei may contribute to brain insulin resistance as a stress-related pathophysiology onset in AD. Piezo2 has been suggested to function as a sensor capable of initiating and modulating ultradian rhythms [9]. It is noteworthy that normally, ultradian oscillations of glucose and insulin are observed under homeostatic conditions [24], whereas in patients with diabetes, the oscillations are attenuated and less controlled [25,26], as is probably the case in AD. In addition, the microbiota-gut-brain and muscle-brain axes may also contribute to insulin resistance downstream of AD pathophysiology in a Piezo2 channelopathy-dependent manner as previously proposed [9]. Consequently, it is not a coincidence that AD is a circadian-related disease, and is often referred to as type 3 diabetes. Therefore, stress-related circadian rhythm disruption [27], underpinned by ultradian rhythm disruption, induces a vicious cycle in AD.

5. Conclusions

Overall, the novel variant of PIEZO2 found in the Hispanic population highlighted a previously unrecognized genetic locus within the PIEZO2 protein structure that may provide insight into how it protects against irreversible Piezo2 channelopathy, which is proposed to initiate AD pathophysiology in the presence of genetic and environmental risk factors. PIP_2 is emerging as a potential treatment for Piezo channelopathy in AD and other neurodegenerative diseases. However, the challenge of targeting the locus of Piezo2 channelopathy within the body-wide Piezo2 system, as well as the precise administration of PIP_2 to the brain and peripheral regions affected by Piezo channelopathy, still remains.

Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CC, cingulate cortex; DAR, defensive arousal response; PIP_2, phosphatidylinositol 4,5-bisphosphate; TBI, traumatic brain injury.

Author Contributions

The single author was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author declares no conflicts of interest.

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