

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

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Abstract

A PIEZO2 variant was shown recently to protect against Alzheimer's disease in the Hispanic population. This analysis implicates the potentially critical role of Piezo2 in Alzheimer's disease pathophysiology. Another recent research mimicked acquired Piezo1 channelopathy by PIEZO1 manipulation. This study also showed that phosphatidylinositol 4,5-bisphosphate (PIP₂) administration ameliorated brain capillary endothelial Piezo1 channelopathy in a mouse model of Alzheimer's disease. However, the initiating microdamage is suggested to be in the prefrontal cortex further upstream of pathophysiology, namely an irreversible Piezo2 channelopathy of glutamatergic terminals that should fine modulate oxytocin release along stressful ultradian events. Implication of Piezo2 in the defensive arousal response reveals an underlying body-wide Piezo2 system of which the proposed prefrontal Piezo2 channelopathy posits a critical locus. PIP₂ is emerging as a potential treatment method of Piezo channelopathy in Alzheimer's disease, however the challenge remains how it could be administered more precisely to affected brain areas.

Keywords: Alzheimer's disease; Piezo2; Piezo2 channelopathy; body-wide Piezo2 system; defensive arousal response; oxytocin; PIP₂

Introduction

A variant of PIEZO2 was shown recently to be protective against Alzheimer's disease (AD) in the Hispanic population [1]. This important analysis implicates the potentially critical role of Piezo2 in AD pathophysiology. Another recent research mimicked acquired Piezo1 channelopathy by point mutation manipulation on PIEZO1 [2]. Moreover, this study also showed that phosphatidylinositol 4,5-bisphosphate (PIP₂) administration ameliorated brain capillary endothelial Piezo1 channelopathy in a mouse model of AD [2].

Noteworthy that inherited variants of PIEZO1 and PIEZO2 have been recognized in certain diseases. However, acquired, but not inherited, Piezo channelopathy, namely acquired Piezo2 channelopathy and its mechanism was first put forward only in 2021 [3]. Two years later, the existence of acquired Piezo2 channelopathy was indeed confirmed in a neurogenetic disease without known pathogenic Piezo2 variants, namely in Angelman syndrome-related research in 2023 [4] and confirmed again in 2025 [5]. In parallel, two genetic analyses on an amyotrophic lateral sclerosis (ALS) cohort, another neurodegenerative disease, indirectly verified its existence first in 2023 [6] and later in 2025 [7]. Furthermore, the critical role of PIP₂ in acquired Piezo2 channelopathy mechanism was published in relation to ALS in 2022 [8]. Even more so, PIP₂ was proposed as a treatment option for acquired Piezo2 channelopathy also in 2022 [9].

Body-Wide Piezo2 System, Prefrontal Piezo2 Channelopathy, Alzheimer's Disease

The initiating pathophysiology of ALS is theorized to be irreversible acquired Piezo2 channelopathy, with underlying genetic and environmental risk factors, or the equivalent of a proton affinity switch on proprioceptive glutamatergic nerve terminals [3,10] and the resultant proprioceptive miswiring may terminally impair the Piezo2-initiated ultradian ultrafast muscle spindle–hippocampal axis [11]. In the case of AD, the irreversible Piezo2 channelopathy-induced impairment of the glutamatergic terminal Piezo2-initiated ultradian ultrafast prefrontal–hippocampal axis is proposed to initiate the disease pathophysiology [11] in the presence of genetic and environmental risk factors. As a result of acquired Piezo2 channelopathy, vesicular glutamate transporter Vglut1 and Vglut2 (glutamate/proton antiports) disconnection is suspected in the acute, chronic and irreversible form [3]. However, irreversible Piezo2 channelopathy may even reduce the expression of Vglut1 and Vglut2, as could be observed in the prefrontal cortex of AD [12]. It has been also proposed that Piezo2-initiated ultradian ultrafast brain axes could be temporarily synchronized to ultradian brain rhythms with hippocampal theta rhythm and medulla firing via long-distance synchronous Piezo2-Piezo2 crosstalk through Vglut2 in a HR dependent fashion [13], constructing the base of an underlying body-wide Piezo2 system.

In support, a traumatic brain injury (TBI) research showed that a body-wide Piezo2 system is operational, reflected in the defensive arousal response (DAR) [14]. DAR is a critical survival mechanism in association with motor abilities and is called forth when an unpredictable threat is perceived by visual and auditory cues [14]. The most prominent significant finding of this research is that genetic intervention showed reduced escape latency and increased escape speed during DAR when PIEZO2 was restituted [14]. Noteworthy, that TBI is a significant risk factor for AD development, especially with repeated incidents. Furthermore, the cingulate cortex (CC), a goal oriented cognitive planning region of the prefrontal cortex, is a critical fast decision making/response locus of DAR along arousal associated threat appraisal where the mix of cognitive control, emotional reactivity and autonomic response result in the decision/response initiation of either “fight or flight” or freeze. Additional important consideration is the bi-directional Vglut2 containing glutamatergic projections of the CC to the eye, ear thalamus and hypothalamus, not to mention to the hippocampus. Moreover, large-fiber glutamatergic afferents projecting from the CC to the thalamus may stand out when it comes to “fight or flight” or freeze appraisal. Indeed, there are cortical glutamatergic afferents from medial prefrontal cortex that are preferentially innervate the converging and segregating excitatory glutamatergic and inhibitory GABAergic calretinin-positive core of paraventricular thalamic nucleus, serving as a “critical bottleneck in the subcortex–cortex communication” [15]. This calretinin positive thalamic core may serve the consciousness to “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 may be especially true if we consider that hippocampal theta wave activation precedes the start of moderate or more intense exercise onset [16], hence hippocampal theta might be on during the “fight or flight” appraisal/decision making process already, leading to moderate or more intense exercise.

The emotional reactivity is suggested by this author to be modulated by the abovementioned Vglut2 containing glutamatergic large fiber afferents from the CC to the paraventricular nuclei of the hypothalamus as well, namely coupling heartbeat pulsatility through the pressure pulse detecting capability of Piezo2, leading to increased oxytocin release based on their terminal efferent function. The proposed modulated cells are the Piezo2 containing oxytocinergic ones in the paraventricular nuclei of the hypothalamus [17]. Oxytocin release associated pathway not only important in social behavior modulation, neuroinflammation and pain suppression, but in arousal as well. It may be telling about the stress-related neurodegenerative microdamage induced lost fine/ultrafast modulation of oxytocin release along this pathway, that the administration of oxytocin proved to be neuroprotective and attenuates both social and non-social memory in AD model [18]. Moreover, it is

evident that CC of the prefrontal cortex is an early target of AD pathology [19]. Consequently, the current author suggest that the age-dependent protein degradation induced Piezo2 channelopathy of the Piezo2 content of the paraventricular nuclei induces Vglut2 disconnection in the CC that in return impairs glutamatergic CC connection to the hippocampal theta rhythm. Moreover, the depletory trajectory leading to irreversible Piezo2 channelopathy and resultant Vglut2 disconnection along this pathway may be the reason why alteration of hippocampal oscillations and theta-gamma coupling is evident prior to A β overproduction in a mouse model of AD [20]. The AD associated hypersynchrony of hippocampal theta is linked to altered glucose metabolism [21] that is suggested by the author of this manuscript to be the consequence of irreversible Piezo2 channelopathy induced proton reversal and resultant OXPHOS depletion [3,10]. In support, CC exhibits the earliest and largest reduction in energy metabolism of the brain [22].

However, the abovementioned acquired Piezo2 channelopathy-induced metabolic and energy generation switch may also come with lipid dysregulation [3,10]. Accordingly, acquired Piezo2 channelopathy may dissociate auxiliary proteins, like TMEM120A/TACAN from Piezo2 due to excessively prolonged excitation under allostatic stress [3,10]. Negatively charged lipids depletion, including cholesterol and PIP₂ due to prolonged Piezo activation may contribute to electrostatic microenvironment charge alteration, eventually leading to proton affinity switch and proton reversal [10]. Off note, the role of APOE4 should be considered in this process as well when it comes to AD, however it is not the subject of this manuscript. Resultant TACAN dissociation may activate phospholipase D and in return it activates lipoxygenase [3]. As an analogy, it has been also put forward earlier that phospholipase C activates lipoxygenase, contributing to the consequence of Piezo1 channelopathy respectively [3]. This analogy could be applied since Piezo2-Piezo1 crosstalk is suspected in a given compartmental microenvironment under homeostatic conditions, while Piezo channelopathy impairs this bi-directional crosstalk [3]. Noteworthy that phospholipase C dysregulated signaling is part of AD pathophysiology [2], likely due to Piezo1 channelopathy. However, the initiating pathophysiology upstream is the proposed prefrontal irreversible Piezo2 channelopathy on glutamatergic terminals in AD [11]. Hence, the aforementioned mimicked acquired Piezo1 channelopathy in AD [2] is suggested to be the direct consequence of the Piezo2 channelopathy-induced impaired Piezo2-Piezo1 crosstalk, leading to neurovascular decoupling. Therefore, the brain capillary endothelial Piezo1 channelopathy is only a downstream pathophysiology of the proposed initiating one. Putting it in other terms, a body-wide Piezo2 system is operational within an even broader body-wide Piezo system that are linked through the compartmental crosstalk between Piezo2 and Piezo1, impacting the co-functioning compartments and the whole-body [3]. Consequently, the brain capillary endothelial Piezo1 channelopathy may reflect a Piezo2 channelopathy within the same or operationally co-functioning compartments [3].

This excessively prolonged excitation under allostatic stress-induced acquired Piezo2 channelopathy on glutamatergic terminals may impair quantum mechanical free energy stimulation aspect of Piezo2-initiated non-synaptic ultrafast synchronous proton signaling through Vglut2 [10], underpinning the proposed ultradian ultrafast brain axes, like the abovementioned ones in AD and ALS [11]. Correspondingly, accumulation of extracellular protons leading to proton affinity switch may posit an increased risk during prolonged excitation under allostatic stress for the aforementioned miswiring towards activated lipoxygenase-induced proton-coupled electron transfer and concerted proton tunneling–electron tunneling [10]. In support, diclofenac attenuates excitation through cyclooxygenase inhibition, but it's lipoxygenase activation blocking may even prevent proton miswiring. This is why diclofenac prevents forced lengthening-induced (analogous to prolonged excitation under allostatic stress) in delayed-onset muscle soreness effectively [10], and may reduce AD risk [23].

Administering high negatively charged PIP₂ could ameliorate Piezo channelopathy by rectifying the electrostatic microenvironment and the unaccounted ultrafast proton signaling, because the positively charged arginine substitution by the applied point mutation of PIEZO1 at critical site [2] seems to be detrimental. Furthermore, PIP₂ is also a nuclear RNA-dependent spatiotemporal

orchestrator through electrostatic interactions [24]. Since acquired Piezo2 channelopathy was suggested to be a principal transcription activator [3,10], therefore Piezo channelopathy associated PIP₂ depletion, or rather nuclear translocation, might essentially contribute to transcription activation due to proton reversal. However, prefrontal glutamatergic terminal irreversible Piezo2 channelopathy-induced impaired ultradian prefrontal–hippocampal axis may not only constantly dysregulate this transcription activation, but might contribute essentially and primarily to hippocampal theta rhythm-related impaired cognition, dysfunctional adult hippocampal neurogenesis, dysregulated systemic inflammation and impairment of long-term spatial memory in AD [11].

Finally, one cardinal symptom of acquired Piezo2 channelopathy is insulin resistance [10,11] as glucose metabolism alteration mentioned above and brain insulin resistance is evident in AD. In support, oxytocin has an immediate positive modulating effect on pancreatic β -cell responsivity and insulin sensitivity [25], therefore the irreversible Piezo2 channelopathy-induced lost fine control of oxytocin release from paraventricular nuclei may contribute to brain insulin resistance as a stress-related initiating pathophysiology in AD. Noteworthy that ultradian oscillations of glucose and insulin is known under homeostatic conditions [26], in contrast to patients with diabetes where the oscillations are attenuated and less controlled [27,28], as 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 was depicted earlier [11]. Consequently, it is not a coincidence that AD is a circadian-related disease, and often named as type 3 diabetes [29], because the stress-related circadian rhythm disruption [30], underpinned by ultradian rhythm disruption, induces a vicious cycle in AD.

Conclusion

Over all, the novel variant of PIEZO2 found in the Hispanic population highlights an important unrecognized genetic locus of the protein structure that may carry significance how it potentially protects against irreversible Piezo2 channelopathy that is suggested to initiate AD pathophysiology in presence of genetic and environmental risk factors. PIP₂ is emerging as a potential treatment method of Piezo channelopathy in AD, and in other neurodegenerative disease. However, the challenge remains how to target the locus of Piezo2 channelopathy within the body-wide Piezo2 system and how it could be administered more precisely to brain and peripheral regions affected by Piezo channelopathy.

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References

1. Willett, J. D. S. et al. Matching heterogeneous cohorts by projected principal components reveals two novel Alzheimer's disease-associated genes in the Hispanic population. *Alzheimers Dement* **22**, e71189, doi:10.1002/alz.71189 (2026).
2. Hashad, A. M., Abd-Alhaseeb, M. M., Lim, X. R., Mathieu, N. M. & Harraz, O. F. PIP₂ corrects an endothelial Piezo1 channelopathy. *Proc Natl Acad Sci U S A* **122**, e2522750122, doi:10.1073/pnas.2522750122 (2025).
3. Sonkodi, B. Acquired Piezo2 Channelopathy is One Principal Gateway to Pathophysiology. *Front Biosci (Landmark Ed)* **30**, 33389, doi:10.31083/FBL33389 (2025).
4. Romero, L. O. et al. Linoleic acid improves PIEZO2 dysfunction in a mouse model of Angelman Syndrome. *Nat Commun* **14**, 1167, doi:10.1038/s41467-023-36818-0 (2023).
5. Romero, L. O. et al. Cofilin Inhibition Ameliorates PIEZO2 and AMPA Dysfunction in a Mouse Model of Angelman Syndrome. *J Neurosci* **45**, doi:10.1523/JNEUROSCI.0965-25.2025 (2025).

6. Nagy, Z. F., Sonkodi, B., Pal, M., Klivenyi, P. & Szell, M. Likely Pathogenic Variants of Ca(v)1.3 and Na(v)1.1 Encoding Genes in Amyotrophic Lateral Sclerosis Could Elucidate the Dysregulated Pain Pathways. *Biomedicines* **11**, doi:10.3390/biomedicines11030933 (2023).
7. Sonkodi, B. et al. Genetic Variants in SDC3, KCNA2, KCNK1, KCNK16, and Heat Shock Transcription Factor-1 Genes: An Exploratory Analysis Supporting the Piezo2 Channelopathy Hypothesis in Amyotrophic Lateral Sclerosis Onset. *International Journal of Molecular Sciences* **26**, 10218 (2025).
8. Sonkodi, B. & Hortobagyi, T. Amyotrophic lateral sclerosis and delayed onset muscle soreness in light of the impaired blink and stretch reflexes - watch out for Piezo2. *Open Med (Wars)* **17**, 397-402, doi:10.1515/med-2022-0444 (2022).
9. Sonkodi, B., Resch, M. D. & Hortobagyi, T. Is the Sex Difference a Clue to the Pathomechanism of Dry Eye Disease? Watch out for the NGF-TrkA-Piezo2 Signaling Axis and the Piezo2 Channelopathy. *J Mol Neurosci* **72**, 1598-1608, doi:10.1007/s12031-022-02015-9 (2022).
10. Sonkodi, B. Delayed-Onset Muscle Soreness Begins with a Transient Neural Switch. *Int J Mol Sci* **26**, doi:10.3390/ijms26052319 (2025).
11. Sonkodi, B. The Microbiota-Gut-Brain Axis in Light of the Brain Axes and Dysbiosis Where Piezo2 Is the Critical Initiating Player. *Int J Mol Sci* **26**, doi:10.3390/ijms26157211 (2025).
12. Kashani, A. et al. Loss of VGLUT1 and VGLUT2 in the prefrontal cortex is correlated with cognitive decline in Alzheimer disease. *Neurobiol Aging* **29**, 1619-1630, doi:10.1016/j.neurobiolaging.2007.04.010 (2008).
13. Langmar, G. et al. Heart Rate Variability Alterations During Delayed-Onset Muscle Soreness-Inducing Exercise-With Piezo2 Interpretation. *Sports (Basel)* **13**, doi:10.3390/sports13080262 (2025).
14. Zhang, Q. et al. Neural mechanism of trigeminal nerve stimulation recovering defensive arousal responses in traumatic brain injury. *Theranostics* **15**, 2315-2337, doi:10.7150/thno.106323 (2025).
15. Biro, L., Buday, Z., Kota, K., Lorincz, S. & Acsady, L. Convergence and Segregation of Excitatory and Inhibitory Afferents in the Paraventricular Thalamic Nucleus. *J Neurosci* **45**, doi:10.1523/JNEUROSCI.0539-25.2025 (2025).
16. Bush, D. et al. Human hippocampal theta power indicates movement onset and distance travelled. *Proc Natl Acad Sci U S A* **114**, 12297-12302, doi:10.1073/pnas.1708716114 (2017).
17. Hamill, O. P. Piezo2 in Paraventricular Neurons: Linking Heartbeat Pulsatility to Increased Oxytocin Release and Social Behavior. *J Integr Neurosci* **24**, 47856, doi:10.31083/JIN47856 (2025).
18. Selles, M. C. et al. Oxytocin attenuates microglial activation and restores social and non-social memory in APP/PS1 Alzheimer model mice. *iScience* **26**, 106545, doi:10.1016/j.isci.2023.106545 (2023).
19. Kiani, I. et al. Posterior cingulate cortex atrophy across the Alzheimer's disease spectrum: A cross-sectional MRI study linking volumetrics to cognitive decline. *J Alzheimers Dis* **109**, 972-979, doi:10.1177/13872877251401612 (2026).
20. Goutagny, R. et al. Alterations in hippocampal network oscillations and theta-gamma coupling arise before Abeta overproduction in a mouse model of Alzheimer's disease. *Eur J Neurosci* **37**, 1896-1902, doi:10.1111/ejn.12233 (2013).
21. Wirt, R. A. et al. Altered theta rhythm and hippocampal-cortical interactions underlie working memory deficits in a hyperglycemia risk factor model of Alzheimer's disease. *Commun Biol* **4**, 1036, doi:10.1038/s42003-021-02558-4 (2021).
22. Valla, J., Berndt, J. D. & Gonzalez-Lima, F. Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. *J Neurosci* **21**, 4923-4930, doi:10.1523/JNEUROSCI.21-13-04923.2001 (2001).
23. Stuve, O., Weideman, R. A., McMahan, D. M., Jacob, D. A. & Little, B. B. Diclofenac reduces the risk of Alzheimer's disease: a pilot analysis of NSAIDs in two US veteran populations. *Ther Adv Neurol Disord* **13**, 1756286420935676, doi:10.1177/1756286420935676 (2020).
24. Sztacho, M. et al. The RNA-dependent association of phosphatidylinositol 4,5-bisphosphate with intrinsically disordered proteins contribute to nuclear compartmentalization. *PLoS Genet* **20**, e1011462, doi:10.1371/journal.pgen.1011462 (2024).
25. Ding, C., Leow, M. K. & Magkos, F. Oxytocin in metabolic homeostasis: implications for obesity and diabetes management. *Obes Rev* **20**, 22-40, doi:10.1111/obr.12757 (2019).

26. Simon, C. & Brandenberger, G. Ultradian oscillations of insulin secretion in humans. *Diabetes* **51 Suppl 1**, S258-261, doi:10.2337/diabetes.51.2007.s258 (2002).
27. O'Meara, N. M., Sturis, J., Van Cauter, E. & Polonsky, K. S. Lack of control by glucose of ultradian insulin secretory oscillations in impaired glucose tolerance and in non-insulin-dependent diabetes mellitus. *J Clin Invest* **92**, 262-271, doi:10.1172/JCI116560 (1993).
28. Sturis, J. et al. Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* **35**, 681-689, doi:10.1007/BF00400263 (1992).
29. Nguyen, T. T., Ta, Q. T. H., Nguyen, T. K. O., Nguyen, T. T. D. & Giau, V. V. Type 3 Diabetes and Its Role Implications in Alzheimer's Disease. *Int J Mol Sci* **21**, doi:10.3390/ijms21093165 (2020).
30. Phan, T. X. & Malkani, R. G. Sleep and circadian rhythm disruption and stress intersect in Alzheimer's disease. *Neurobiol Stress* **10**, 100133, doi:10.1016/j.ynstr.2018.10.001 (2019).

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