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Editorial

Piezo channels as molecular gatekeepers: A review of their involvement in alzheimer's disease

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1. Introduction

Alzheimer's disease (AD) stands as a complex neurodegenerative disorder, characterized by progressive cognitive decline and memory impairment. Despite decades of research, a comprehensive understanding of its pathophysiology remains elusive. The amyloid cascade theory has long been considered the prevailing model, positing that the accumulation of beta-amyloid (Aβ) peptides initiates a cascade of events leading to neuronal dysfunction and eventual cognitive decline.[1] However, the translation of this theory into effective therapeutic interventions has been met with limited success, rendering poor prognostic outcomes for the patients.

In light of the challenges associated with existing treatment modalities, there is a compelling necessity for innovative and targeted approaches to address the multifaceted nature of AD. This has sparked a renewed interest in exploring alternative molecular pathways that contribute to neurodegeneration. One such emerging avenue is the investigation of Piezo channels, mechanosensitive ion channels implicated in various physiological processes. Piezo channels, first identified for their role in cellular mechanotransduction, have garnered attention for their potential involvement in neurodegenerative processes. These channels are activated by physical forces, allowing the influx of cations, particularly calcium ions.[2] This editorial aims to provide a comprehensive overview of the role of Piezo channels in Alzheimer's disease, shedding light on their mechanistic connections with neurodegeneration. By exploring the intricate interplay between Piezo channels and key cellular pathways, we seek to unravel their potential as novel therapeutic targets for mitigating the devastating effects of Alzheimer's disease. In doing so, we aspire to contribute to the ongoing efforts in advancing our understanding of AD pathogenesis and facilitating the development of targeted interventions with improved clinical outcomes.

2. Mechanosensation in the Brain: A New Paradigm

The mechanosensation in the brain holds significant importance, considering the brain's unique viscoelastic response and its essential role in regulating brain function and disease. Traditionally, neuroscience has primarily focused on genetic, biochemical signals, and electrophysiology, but recent evidence underscores the pivotal role of mechanical signals in these processes.[3] Mechanical signals in the cell microenvironment are increasingly recognized for their regulatory roles in

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physiological processes and disease progression within the brain. Mechanical forces influence normal physiological neuronal network activity, axonal extension, neuron-astrocyte communication, and interactions between neurons and substrates. Changes in the mechanical properties of the extracellular matrix (ECM) are implicated in brain aging, brain tumors, Alzheimer's disease (AD), and other neurodegenerative diseases[4]. Mechanical signals induce the formation of a specific stiffness gradient in brain tissue, determined by ECM molecules and cells embedded in the ECM. This gradient influences the behavior and function of various cell types in the brain, including neurons, astrocytes, and microglia. The stiffness of the matrix, measured by elastic modulus, and the roughness of the ECM's surface structure impact neuronal and glial cell growth and function. The mechanotransduction process, converting extracellular mechanical signals into intracellular electrochemical signals, is crucial for understanding how mechanical cues influence brain function.[5]

The Piezo receptor family, distributed widely in the central nervous system (CNS), plays a vital role in mechanotransduction. The Piezo1 channel, a mechanosensitive ion channel protein located on the membrane surface, is particularly important for neurophysiological processes under homeostasis. These processes include neuronal growth, axon extension, glial cell migration, regulation of glial cell responsiveness, and the activation of CNS resident immune cells.[6] Moreover, Piezo1 is implicated in neuropathological conditions, such as Alzheimer's disease and brain tumors, showcasing its diverse roles in neuro(patho)physiology. Understanding the basic properties of Piezo1 and its role in the CNS provides valuable insights into the complex interplay between mechanical signals and brain function, opening avenues for potential interventions in central nervous system diseases.[7,8]

3. Piezo Channels in Synaptic Function: Bridging the Mechanical Gap

Mechanosensation of Piezo1, the largest known pore-type ion channel, plays a pivotal role in transducing mechanical forces into intracellular electrochemical signals. Piezo1 was first identified in 2010 as a mechanically gated channel protein capable of sensing mechanical forces in mammalian Neuro2a cells.[9] Upon mechanical activation, Piezo1 facilitates the influx of extracellular cations, including Ca2+, Na+, and K+, initiating intracellular second messenger pathways and propagating electrical signals (Figure 1). Structural insights into Piezo1 reveal a complex arrangement, consisting of three homotrimeric proteins forming a propeller bladelike structure. This unique topology positions the central pore as the site responsible for cation influx, while the three peripheral blades serve as the key area for sensing mechanical forces. The trimeric Piezo1 structure is the foundation for understanding how the channel translates mechanical signals into intracellular electrochemical responses. Piezo1 channels exhibit three distinct states: closed, open, and inactivated. At rest, Piezo1 is embedded in the cell membrane, with the propeller bending outward to close the central ion channel. Transient mechanical signals induce Piezo1 to open reversibly, followed by complete inactivation within 100 ms. The mechanism involves the three propeller blades opening the central pore in response to membrane stress, generating a mechanically activated cationic current.[10]

The activation of Piezo1 is intricately linked to the mechanical properties of the cell membrane. The channel senses mechanical indentation and tension, translating cell-side membrane tension into conformational changes that drive channel activation. Moreover, the composition of the membrane, specifically the ratio of saturated to polyunsaturated fatty acids, influences Piezo1 activation and inactivation dynamics. Additionally, an intact cytoskeleton is demonstrated to be crucial for Piezo1 responsiveness to mechanical pressure. Interestingly, Piezo1 is not solely responsive to mechanical cues.[11] Extracellular H+ concentrations and low-pH environments induce Piezo1 inactivation, suggesting a broader sensitivity to environmental factors beyond membrane mechanics. Collectively, these findings underscore the sophisticated mechanisms by which Piezo1 serves as amolecular sensor, enabling cells to perceive and respond to diverse mechanical and chemical signals in their microenvironment.

4. Piezo Channels in Alzheimer's Disease: Connecting the Dots

The role of Piezo1 in Alzheimer's disease (AD) is implicated in the regulation of the inflammatory response of immune cells, particularly microglia. In the context of AD, microglia, as resident macrophages of the brain, assume distinct phenotypes denoted as classical activation (M1) and alternate activation (M2). Notably, Piezo1 expression in microglia is subject to modulation in AD, influenced by factors such as cell clustering and racial differences. Analysis of single-cell RNA sequencing and single nuclei datasets reveals that Piezo1 exhibits a dynamic expression pattern in AD. Specifically, Piezo1 is downregulated in the disease-associated microglia (DAM) of 5×FAD mouse datasets but upregulated in the human AD-specific subcluster M1.[12] The activation of Piezo1 is intricately linked to the microglial phenotype, with its expression affected by the stiffness and roughness of the extracellular matrix.[13] Increased surface roughness and stiffness tend to drive microglia towards the pro-inflammatory M1 phenotype, characterized by elevated levels of interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α). Notably, the knockout of Piezo1 inhibits the release of pro-inflammatory factors from

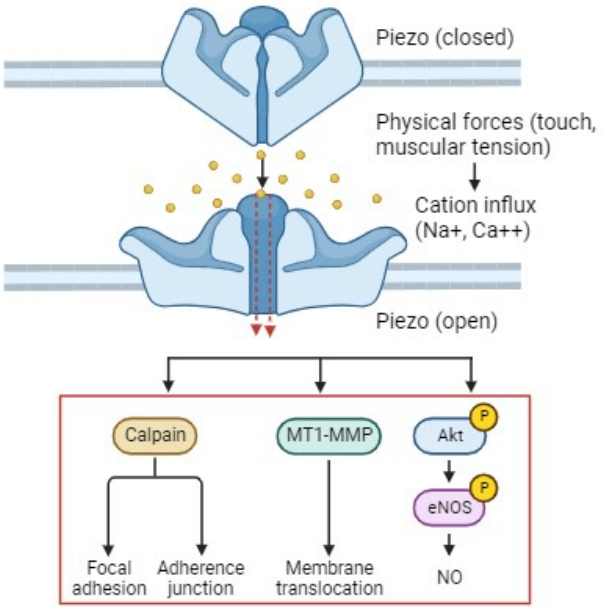

Figure 1: A schematic representation of the activation mechanism of Piezo channels through physical forces. Upon activation, Piezo channels allow an influx of cations, initiating various calcium-dependent pathways such as calpain and Akt. This cascade leads to membrane translocation and the release of nitric oxide (NO), shedding light on the intricate cellular responses triggered by piezo channels.

microglia, suggesting a role for Piezo1 in regulating the inflammatory response mediated by a stiff substrate.[14] In the brain, the activation of Piezo1 in the presence of inflammation-stimulating factors such as amyloid-beta (Aβ) or lipopolysaccharide (LPS) tends to suppress the pro-inflammatory phenotype of glial cells. Mechanistically, Piezo1 exerts an anti-inflammatory effect by inhibiting the NF-κB pathway, without impacting the extracellular signal-regulated kinase (ERK) and p38 pathways.[15] This anti-inflammatory influence is demonstrated through the inhibition of LPS-induced microglial activation and the production of pro-inflammatory factors TNF-α and IL-6. However, conflicting results have been reported regarding the impact of Piezo1 activation on pro-inflammatory cytokine release, with studies indicating both inhibitory and stimulatory effects depending on the experimental conditions, including the concentration of the Piezo1 activator Yoda.[16]

5. Challenges and Future Directions

While in vitro studies have provided valuable insights into the role of Piezo1 in regulating the inflammatory phenotype of microglia, further research is warranted to elucidate the in vivo implications of Piezo1 activation. Decoding the role of Piezo channels in AD pathogenesis not only expands our comprehension but also paves the way for therapeutic innovation. Targeting these channels emerges as a promising strategy to modulate mechanosensation within the intricate neural landscape, potentially offering a means to alleviate cognitive decline in AD. The prospect of developing pharmacological agents that selectively influence Piezo channels holds the promise of a breakthrough in AD treatment, presenting a novel avenue for intervention that addresses the mechanistic underpinnings of the disease and may usher in a new era of targeted therapeutics for individuals grappling with this challenging neurodegenerative disorder.

6. Conclusion

In conclusion, the exploration of Piezo1 channels emerges as a promising avenue in advancing our comprehension of Alzheimer's disease (AD). As we delve deeper into the intricate landscape of AD pathophysiology, it becomes increasingly apparent that mechanical forces play a crucial role in the regulation of neurodegenerative processes. Piezo1 channels, with their ability to sense and transduce mechanical signals, offer a unique perspective on the interplay between cellular mechanics and the progression of AD.

The studies discussed underscore the significance of Piezo1 channels in various facets of neurobiology, from neuronal growth and development to glial cell responsiveness and immune cell activation. Particularly intriguing is the connection between Piezo1 and the mechanical properties of the brain microenvironment, shedding light on how these channels may influence the progression of AD in the context of altered matrix stiffness and roughness.

7. Source of Funding

None.

8. Conflict of Interest

None.

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