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Mini Review

δ-Subunit GABAA Receptors and Tonic Inhibition: Implications for Sedation and Anesthetic Mechanisms

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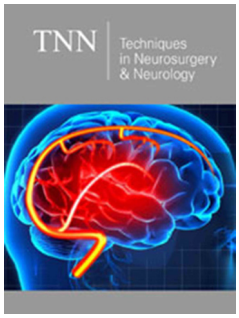

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Abstract

GABAA receptors (GABAA_AA) are ligand-gated chloride channels mediating fast and slow inhibitory signaling in the nervous system. δ-Subunit-containing receptors exhibit high GABA affinity, extrasynaptic localization and marked sensitivity to endogenous neurosteroids, generating tonic inhibitory currents that regulate baseline excitability in the CNS. Emerging evidence indicates that these receptors are also expressed in peripheral tissues, including the skin, retina, olfactory epithelium, gastrointestinal tract, kidney, immune cells and reproductive organs. They are notably absent in the heart, highlighting a selective role in sensory modulation. We hypothesize that δ-subunit-containing GABAA_AA receptors mediate local and systemic sensory inhibition through tonic, extrasynaptic signaling and neurosteroid-dependent modulation. This network stabilizes neuronal and sensory activity, prevents hyperexcitability and may coordinate body-wide sensory responsiveness. Dysregulation of this system could contribute to disorders such as chronic pain, inflammatory skin disease, olfactory dysfunction and neuropsychiatric conditions.

Keywords: δ-subunit GABAA receptors; Tonic inhibition; Extrasynaptic signaling; Neurosteroids; Peripheral sensory modulation; CNS regulation; Sensory hyperexcitability

Introduction

GABAA receptors (GABAA_AA) are chloride-selective ligand-gated ion channels that mediate inhibitory signaling throughout the Central Nervous System (CNS). Among their subtypes, δ-subunit-containing receptors are distinguished by high GABA affinity, extrasynaptic localization and sensitivity to endogenous neurosteroids [1-4]. In the CNS, these receptors generate tonic inhibitory currents that stabilize neuronal firing, regulate network oscillations and modulate baseline excitability [1,3,4]. Unlike synaptic γ-subunit-containing receptors, δ-containing GABAA_AA receptors are poorly responsive to benzodiazepines and specialized for continuous, rather than phasic, inhibition [2,3]. Although initially considered CNS-specific, δ-containing GABAA_AA receptors are now detected in multiple peripheral tissues, including the skin, retina, olfactory epithelium, gastrointestinal tract, kidney, immune cells and reproductive organs [5-9]. These tissues are regularly exposed to mechanical, chemical or inflammatory stimuli and require mechanisms to suppress baseline excitability and prevent sensory overload. In contrast, δ-containing receptors are absent in cardiomyocytes, consistent with the heart's reliance on continuous depolarization and precise excitatory conduction [5,9].

Hypothesis

We propose that δ-subunit-containing GABAA_AA receptors mediate local sensory inhibition in peripheral tissues and coordinate systemic sensory inhibition through tonic, extrasynaptic signaling mechanisms analogous to those in the CNS. This system is likely modulated by circulating neurosteroids, establishing a body-wide inhibitory tone that

prevents sensory hyperexcitability under stress or pathological conditions . This hypothesis provides a unifying framework for understanding how δ-containing receptors regulate excitability across central and peripheral tissues. In the skin, keratinocytes and resident immune cells produce and respond to GABA, with tonic GABAergic signaling regulating itch, pain, inflammation and epidermal homeostasis [6,10,11]. In sensory organs such as the retina and olfactory epithelium, tonic inhibition maintains optimal signal-to-noise ratios during sustained stimulation [7,8,12]. The high GABA affinity and extrasynaptic distribution of δ-containing receptors make them well suited to suppress low-level, persistent sensory input and prevent hyperexcitability, supporting their hypothesized role. δ-Containing GABAA_AA receptors are highly sensitive to endogenous neurosteroids, including allopregnanolone and tetrahydrodeoxycorticosterone [4,13]. Fluctuations in neurosteroid levels due to stress, hormonal changes, inflammation or disease may synchronously modulate receptor activity across tissues, producing a coordinated inhibitory tone. This mechanism could dampen global sensory responsiveness and prevent sensory overload. The absence of δ-containing GABAA_AA receptors in cardiac tissue reinforces their specialization for sensory regulation rather than continuous excitatory activity [5,9]. Enrichment in sensory, epithelial, immune and neural tissues reflects an evolutionarily conserved mechanism to stabilize excitability and prevent peripheral hyperactivity.

Conclusion

δ-Subunit-containing GABAA_AA receptors form a distributed, neurosteroid-sensitive inhibitory network spanning central and peripheral tissues. Our hypothesis-that these receptors mediate both local and systemic sensory inhibition-explains their functional specialization and tissue distribution. By suppressing baseline excitability, preventing peripheral sensitization and coordinating global sensory responsiveness, δ-containing receptors may maintain normal sensory homeostasis and mitigate hyperexcitability under stress. Dysregulation of this network could contribute to sensory amplification disorders, including chronic pain, inflammatory skin disease, olfactory dysfunction and neuropsychiatric conditions. Future studies combining tissue-specific receptor mapping, neurosteroid manipulation and functional sensory assays are essential to validate this hypothesis and explore therapeutic interventions targeting tonic inhibition [14-16].

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