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Influence of 5-HT2 Receptor Blockade on Motor Unit Firing and Persistent Inward Currents in Humans during Voluntary Muscle Contraction

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Abstract

Serotonergic neuromodulation plays a role in enhancing voluntary muscle activation. However, the influence of the potential motoneuron receptor candidate (5-HT2) on the firing rate and activation threshold of motor units (MUs) in humans remains uncertain. This study aimed to investigate the impact of 5-HT2 receptor activity on human MU behavior during gradually increasing contractions of varying intensity. The tibialis anterior muscle's high-density surface electromyography (HDsEMG) was recorded while participants performed ramped isometric dorsiflexions at 10%, 30%, 50%, and 70% of their maximum voluntary contraction (MVC). MU characteristics were extracted from HDsEMG data collected from 11 young adults (including four females) before and after taking either an 8 mg cyproheptadine dose or a placebo. Blocking 5-HT2 receptors led to a decrease in MU discharge rate during steady-state muscle activation, regardless of the contraction intensity ($P<0.001$; estimated mean difference (Δ)=1.06 pulses/s). Additionally, there was an elevated MU derecruitment threshold ($P<0.013$, Δ=1.23% MVC), while maximal voluntary contraction force remained unchanged ($P=0.652$). At 10% MVC ($P<0.001$, Δ=0.99 Hz) and 30% MVC ($P=0.003$, Δ=0.75 Hz), there was a reduction in estimates of persistent inward current amplitude, aligning with changes in MU firing behavior attributed to 5-HT2 receptor antagonism. Overall, these findings underscore the role of 5-HT2 receptor activity in regulating discharge rate among groups of spinal motoneurons during voluntary contractions. This study offers evidence of a direct connection between MU discharge properties, persistent inward current activity, and 5-HT2 receptor activity in humans.

Keywords: Dendrites • Antagonism • Motoneurones

Introduction

The intricate interplay between the nervous and muscular systems governs our ability to perform voluntary movements. One key neurotransmitter involved in this process is serotonin (5-HT), which acts on various receptors, including the 5-HT2 receptor subtype. Recent research has shed light on the role of 5-HT2 receptors in modulating motor unit firing and the estimation of persistent inward currents during voluntary muscle contraction in humans. Understanding these mechanisms could have significant implications for unraveling the complexities of neuromuscular control and potentially lead to therapeutic advancements in motor function-related disorders. Serotonin, commonly known as the "feel-good" neurotransmitter, plays a multifaceted role in the nervous system. In addition to its involvement in mood regulation, sleep, and appetite, serotonin also exerts influence on motor function. The 5-HT2 receptor subtype, a member of the G-protein coupled receptor family, has garnered particular interest due to its presence in both the central nervous system and peripheral tissues, including skeletal muscles [1-3].

Description

Motor unit firing and voluntary muscle contraction

Motor units are fundamental components of the neuromuscular system, comprising a motor neuron and the muscle fibers it innervates. Voluntary muscle contractions involve the recruitment and firing of motor units to generate force and produce movement. The firing rate of motor units is a critical factor in determining the strength and precision of muscle contractions [4].

Persistent Inward Currents (PICs)

Persistent Inward Currents (PICs) are subthreshold currents that can contribute to the excitability of motor neurons. These currents are implicated in various neuromuscular disorders and can significantly impact motor unit behavior. PICs are thought to play a role in sustaining motor neuron firing during weak synaptic input, contributing to the generation of rhythmic motor patterns and influencing muscle tone [5].

The link between 5-HT2 receptors and motor unit firing

Recent studies have begun to unravel the intricate relationship between 5-HT2 receptors and motor unit firing. Blockade of 5-HT2 receptors has been shown to suppress motor unit firing during voluntary muscle contractions. This suggests that serotonin, acting through the 5-HT2 receptor subtype, modulates the excitability of motor neurons, potentially affecting motor unit recruitment and force production.

Role of 5-HT2 receptor blockade in persistent inward currents

Emerging evidence also points to the involvement of 5-HT2 receptors in regulating PICs. Blockade of 5-HT2 receptors appears to influence the magnitude of PICs, which could have implications for motor unit firing patterns and the overall control of muscle contraction. The exact mechanisms underlying this relationship are still being investigated, but it is becoming increasingly clear that serotonin and 5-HT2 receptors play a significant role in shaping PICs.

Clinical implications

The insights gained from studying the blockade of 5-HT2 receptors and

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its effects on motor unit firing and PICs hold promise for potential clinical applications. Understanding these mechanisms could lead to novel therapeutic strategies for conditions characterized by altered neuromuscular control, such as neuromuscular disorders, movement disorders, and even rehabilitation after injuries. Targeted interventions that modulate 5-HT2 receptor activity could help fine-tune motor unit firing patterns and enhance muscle function [6].

Conclusion

The blockade of 5-HT2 receptors has emerged as a key player in modulating motor unit firing and persistent inward currents during voluntary muscle contraction in humans. As our understanding of these intricate processes continues to evolve, the potential for therapeutic interventions to optimize neuromuscular control becomes increasingly promising. This research not only sheds light on the fundamental mechanisms of motor function but also paves the way for innovative treatments that could significantly impact the lives of individuals with motor-related disorders.

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Conflict of Interest

None.

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