Role of D1R modulation of the I_h current in Rhythmic Spinal Mammalian Motor Networks

Grace Lee, Class of 2022

Restless Legs Syndrome (RLS) is a chronic disorder largely characterized by hyperarousal, periodic leg movements during sleep (PLMS), and unpleasant sensory symptoms ("urge to move") at rest. Brain iron deficiency (BID) is most likely a cause of PLMS in RLS because of its association with hyper-dopamine and hypo-adenosine systems in the basal ganglia (Ferré et al., 2018). However, we still are uncertain of the exact functional role BID has on the directional connections between dopaminergic and adenosinergic neurotransmission, especially in the spinal cord, where motor networks controlling movement are found. The spinal cord houses all the dopamine and adenosine receptors essential for locomotion. More specifically, the motor neurons (MNs) of the spinal cord consist of excitatory G_s-coupled dopamine D1 receptors (D1Rs) and inhibitory G_i-coupled adenosine A1 receptors (A1Rs) that postsynaptically reduce D1R-mediated excitability through a functional A1R-D1R heteromer formation (Rivera-Oliver et al., 2018). Furthermore, D1Rs control spinal MN excitability by increasing cyclic adenosine monophosphate (cAMP) concentration and opening hyperpolarization-activated cyclic nucleotide-gated non-selective cation channel type 1 (HCN1) (Rivera-Oliver et al., 2018).

Our study aims to elucidate the importance of the D1 receptor subtype on modulating the hyperpolarization-activated cation current (I_h) in spinal mammalian motor networks. We hypothesized that blocking I_h in the presence of a D1 agonist (enhanced dopaminergic modulation) would increase the cycle period and disrupt bursting stability. Neonatal (P0-P5; n = 7) mouse spinal cord preparations were used to measure amplitude, duration, and cycle period of extracellular ventral root (L2 and L5) recordings via suction electrodes. Treatment conditions include serotonin (9-15μM 5HT) and N-methyl-D-aspartate (6 μM NMDA) with and without a D1 agonist (10μM SKF38393) to assess the effect of D1R on rhythmic bursting. Subsequently, an I_h blocker (1μM ZD7288) was added to observe the importance of I_h in modulating MN burst activity. For both L2 and L5 roots, blocking the I_h current led to significant increases in burst amplitude, duration, and cycle period in respect to the control 5HT/NMDA condition. Our results propose that D1Rs play a significant role in modulating I_h by increasing cAMP levels and opening HCN1 channels at a more depolarized membrane potential. Future experiments involve analyzing the effect of disrupting A1R-D1R heteromers in spinal MNs and seeing its effects on motor bursting via the use of receptor-specific transmembrane disrupting peptides.

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