Dopamine modulates hyperpolarization-activated inward current in spinal motoneurons

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Restless Legs Syndrome (RLS) is a sensorimotor disorder with common symptoms including an irresistible urge to move the legs, period leg movements during sleep, and uncomfortable leg sensations. Accumulating evidence demonstrates an increased excitability of spinal motoneurons in patients with RLS, which is largely dependent on the activity of ion channels. Specifically, the hyperpolarization-activated inward current (I_h), a nonselective cation current activated by membrane hyperpolarization, permits the influx of cations to not only return the membrane to its resting potential but also gives it a boost towards the threshold to generate and maintain rhythmic activity. These channels are in turn subject to modulation by various neurotransmitters, such as dopamine. Dopamine has shown to activate adenylyl cyclase and enhance the cellular production of cyclic adenosine monophosphate (cAMP) by binding to the D_1 receptor (D_1R). cAMP acts as a secondary messenger within the cell and binds to the I_h channel, which contains a direct binding site for the molecule. Therefore, this project aimed to examine to role of I_h and its modulation by dopamine in the mammalian central pattern generator (CPG) network for hindlimb locomotion to yield valuable clinical insights in advancing the design and development of RLS curative treatments.

In vitro neonatal (0-5 days old) mouse spinal cords were isolated via ventral laminectomy, and fictive locomotion was evoked through the perfusion of serotonin (5-HT) and N-methyl-d-aspartate (NMDA). Two specific muscle activities were measured using suction electrodes, specifically the flexor activity (controlled by L1/2 roots) and the extensor activity (L5 roots). The obtained recordings can be rectified and smoothed, from which three parameters (i.e., burst duration, cycle period, and burst amplitude) were analyzed. The project involved two experiments. In the first experiment, the preparations were treated with an I_h blocker (ZD7288) to assess the role of I_h in modulating the motoneuron burst activity. In the second experiment, the spinal cords were treated first with a D_1R agonist (SKF 38393) and then with ZD7288 to investigate the role of I_h in a dopamine-modulated system. The results showed that ZD7288 increased burst amplitude, burst duration, and cycle period in both flexors and extensors, suggesting that blocking I_h slows down the rhythmic activity by decreasing the overall excitability at the CPG level. Meanwhile, SKF38393 was shown to decrease burst amplitude, burst duration, and cycle period in both flexors and extensors; the subsequent application of ZD7288 counteracted these excitatory effects. It appeared that SKF38393 accelerated the rhythmic motor network, reinforcing the idea that dopamine modulates I_h in a D_1R-dependent mode of action. Future steps will involve replicating these experiments with different concentrations of ZD78288 to examine its potential dose-dependent effects and applying dopamine at varying concentrations to confirm the D_1R-specific nature of dopamine modulation.

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References

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