## It takes two to tango: the persistent sodium current swings with M-current in synchronizing locomotor movements

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The sculpture 'The Walking Man' by Rodin elegantly captures the essence of walking: a naturally fluid and often unconscious motor behavior primarily orchestrated by the spinal cord. Our research, drawing parallels with the yin and yang principles, has identified two opposite currents crucial for automating locomotion. Within the central pattern generator (CPG) for locomotion in mice, we found interneurons that inherently oscillate at stepping rhythm frequencies (Brocard et al., 2013; Neuron). Key to these oscillations is the persistent sodium current (INaP). The cessation of locomotor-like activities upon the blockade INaP, led us to posit that locomotion relies on circuits incorporating INaP as a 'pacemaker' current. One aspect our research is identifying the origin of INaP. We indicate that Nav1.6 channels, in synergy with Nav1.1, are crucial in supporting INaP, pacemaker activities and the locomotor rhythm (Drouillas et al., 2023, Cell reports). We further identified a persistent K+ conductance, characteristic of the M-current (IM), mediated by Kv7.2 channels, which counterbalances INaP (Verneuil et al., 2020; Plos Biol). The dynamic interaction between INaP and IM appears to be a fundamental mechanism in setting locomotion speed. Beyond the CPG, this partnership regulates spinal motoneurons, which execute CPG commands. The cyclic activation of INaP enhances motoneuron gain, boosting locomotor output, while IM provides a regulatory counterforce. Importantly, INaP mediated by Nav1.6 in lumbar motoneurons is important for hindlimb posture (Bos et al., 2021; Nature Com). Overall, the INaP/IM interplay is central to the locomotor network, essential for effective and adaptive walking. The imbalance between the two leads to significant motor issues, like spasticity after a spinal cord injury (Brocard et al., 2016; Nature Med; Kerzoncuf et al., 2024; Molecular Therapy in press).