Modulators targeting fast-activating transient K+ conductance shape subthalamic burst discharges

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Background: Excessive subthalamic bursts may impair information coding by the basal ganglia and result in the cardinal symptoms of Parkinson disease (PD). Burst discharges usually comprise repetitive spikes on top of a timely-terminated depolarizing plateau. We have previously shown that modulation of a slowly-activating hyperpolarizing K+ conductance may change the length of each burst as well as the timing of subsequent bursts in the subthalamic nucleus. Here we endeavor to elucidate the role of fast-activating transient K+ conductances in shaping the subthalamic bursts.

Methods: Brain slices containing the subthalamic nucleus were prepared from C57BL/6 mice (aged p18-25) or normal/parkinsonian rats (aged p32-46). The subthalamic neurons were recorded in whole-cell current-clamp mode with 3-6 megaohm pipettes filled with K+-based solution (in mM, 116 KMeSO4, 6 KCl, 2 NaCl, 20 HEPES, 0.5 EGTA, 4 MgATP, 0.3 NaGTP, 10 NaPO4 creatine, and pH 7.25 adjusted with KOH). During recording, the slice was continuously perfused with oxygenated saline (in mM, 125 NaCl, 26 NaHCO3, 25 glucose, 2.5 KCl, 1.25 NaH2PO4, 1 MgCl2, and 2 CaCl2) in the presence or absence of different pharmacological agents at a constant flow rate ~5 ml/min controlled by a peristaltic pump. Recordings were acquired with a Multiclamp 700B, filtered at 5 kHz, and digitized at 10-20 kHz with a Digidata-1440 analog/digital interface along with pCLAMP software (MDS Analytical Technologies).

Results: A fast-activating transient K+ conductance made available by hyperpolarization critically suppresses not only transient membrane depolarization (and thus burst discharges), but also the reliability of burst-determining excitatory input (and thus information relay of neurons). Furthermore, the increased burst discharges by pharmacologically- or genetically-manipulated fast-activating K+ conductance in the subthalamic nucleus could be correlated with the electrophysiological and behavioral features in the animal models of PD.

Conclusion: Modulators of fast-activating K+ conductance affect the reliability of cortico-subthalamic transmission and likelihood of subthalamic burst generation, and thus could play a decisive role in membrane excitability as well as propagation of physiological and pathophysiological brain rhythms.