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Computational modeling of spike generation in serotonergic neurons of the dorsal raphe nucleus

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ABSTRACT

Serotonergic neurons of the dorsal raphe nucleus, with their extensive innervation of limbic and higher brain regions and interactions with the endocrine system have important modulatory or regulatory effects on many cognitive, emotional and physiological processes. They have been strongly implicated in responses to stress and in the occurrence of major depressive disorder and other psychiatric disorders. In order to quantify some of these effects, detailed mathematical models of the activity of such cells are required which describe their complex neurochemistry and neurophysiology. We consider here a single-compartment model of these neurons which is capable of describing many of the known features of spike generation, particularly the slow rhythmic pacemaking activity often observed in these cells in a variety of species. Included in the model are 11 kinds of ion channels: a fast sodium current I_{Na}, a delayed rectifier potassium current I_{KDR}, a transient potassium current I_A, a slow non-inactivating potassium current I_M, a low-threshold calcium current I_T, two high threshold calcium currents I_L and I_N, small and large conductance potassium currents I_{SK} and I_{BK}, a hyperpolarization-activated cation current I_H and a leak current I_{Leak}. In Sections 3–8, each current type is considered in detail and parameters estimated from voltage clamp data where possible. Three kinds of model are considered for the BK current and two for the leak current. Intracellular calcium ion concentration Ca_i is an additional component and calcium dynamics along with buffering and pumping is discussed in Section 9. The remainder of the article contains descriptions of computed solutions which reveal both spontaneous and driven spiking with several parameter sets. Attention is focused on the properties usually associated with these neurons, particularly long duration of action potential, steep upslope on the leading edge of spikes, pacemaker-like spiking, long-lasting afterhyperpolarization and the ramp-like return to threshold after a spike. In some cases the membrane potential trajectories display doublets or have humps or notches as have been reported in some experimental studies. The computed time courses of I_A and I_T during the interspike interval support the generally held view of a competition between them in influencing the frequency of spiking. Spontaneous activity was facilitated by the presence of I_H which has been found in these neurons by some investigators. For reasonable sets of parameters spike frequencies between about 0.6 Hz and 1.2 Hz are obtained, but frequencies as high as 6 Hz could be obtained with special parameter choices. Topics investigated and compared with experiment include shoulders, notches, anodal break phenomena, the effects of noradrenergic input, frequency versus current curves, depolarization block, effects of cell size and the effects of I_M. The inhibitory effects of activating 5-HT1A autoreceptors are also

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); 5-HTP, 5-hydroxytryptophan; ACh, acetylcholine; AHP, afterhyperpolarization; BK, big potassium channel; Ca_i, internal calcium ion concentration; CB, calbindin-D28k; CBP, calcium binding protein; CDI, calcium-dependent inactivation; CNS, central nervous syytem; CR, calretinin; CRF, corticotropin releasing factor; CSF, calcium source factor; D, duration (of spike); DA, dopamine; DRN, dorsal raphe nucleus; EC_{50}, concentration of drug causing half-maximal response; EPSP, excitatory post-synaptic potential; FURA-2AM, Fura-2-acetoxymethyl ester; GABA, gamma-aminobutyric acid; HPA, hypothalamus-pituitary-adrenal cortex; GIRK, G-protein-coupled inwardly rectifying K^+; HVA, high-voltage activated; ISI, interspike interval; LVA, low-voltage activated; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; PV, parvalbumin; REM, rapid eye movement; SE, serotonin or serotonergic; SK, small potassium channel; SSRI, selective serotonin re-uptake inhibitor; TEA, tetra-ethyl ammonium chloride; TPH, tryptophan hydroxylase; TTX, tetrodotoxin; VGCC, voltage-gated calcium channel.

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investigated. There is a considerable discussion of in vitro versus in vivo firing behavior, with focus on the roles of noradrenergic input, corticotropin-releasing factor and orexinergic inputs. Location of cells within the nucleus is probably a major factor, along with the state of the animal.

Contents

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