Reduced availability of voltage-gated sodium channels by depolarization or blockade by tetrodotoxin boosts burst firing and catecholamine release in mouse chromaffin cells

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Résumé en anglais	KEY POINTS: Mouse chromaffin cells (MCCs) of the adrenal medulla possess fast-inactivating Nav channels whose availability alters spontaneous action potential firing patterns and the Ca2+ -dependent secretion of catecholamines. Here, we report MCCs expressing large densities of neuronal fast-inactivating Nav1.3 and Nav1.7 channels that carry little or no subthreshold pacemaker currents and can be slowly inactivated by 50% upon slight membrane depolarization. Reducing Nav1.3/Nav1.7 availability by tetrodotoxin or by sustained depolarization near rest leads to a switch from tonic to burst-firing patterns that give rise to elevated Ca2+ -influx and increased catecholamine release. Spontaneous burst firing is also evident in a small percentage of control MCCs. Our results establish that burst firing comprises an intrinsic firing mode of MCCs that boosts their output. This occurs particularly when Nav channel availability is reduced by sustained splanchnic nerve stimulation or prolonged cell depolarizations induced by acidosis, hyperkalaemia and increased muscarine levels. ABSTRACT: Action potential (AP) firing in mouse chromaffin cells (MCCs) is mainly sustained by Cav1.3 L-type channels that drive BK and SK currents and regulate the pacemaking cycle. As secretory units, CCs optimally recruit Ca2+ channels when stimulated, a process potentially dependent on the modulation of the AP waveform. Our previous work has shown that a critical determinant of AP shape is voltage-gated sodium channel (Nav) channel availability. Here, we studied the contribution of Nav channels to firing patterns and AP shapes at rest (-50 mV) and upon stimulation (-40 mV). Using quantitative RT-PCR and immunoblotting, we show that MCCs mainly express tetrodotoxin (TTX)-sensitive, fast-inactivating Nav1.3 and Nav1.7 channels that carry little or no Na+ current during slow ramp depolarizations. Time constants and the percentage of recovery from fast inactivation and slow entry into closed-state inactivation are similar to that of brain Nav1.3 and Nav1.7 channels. The fraction of available Nav channels is reduced by half after 10 mV depolarization from -50 to -40 mV. This leads to low amplitude spikes and a reduction in repolarizing K+ currents inverting the net current from outward to inward during the after-hyperpolarization. When Nav channel availability is reduced by up to 20% of total, either by TTX block or steady depolarization, a switch from tonic to burst firing is observed. The spontaneous occurrence of high frequency bursts is rare under control conditions (14% of cells) but leads to major Ca2+ -entry and increased catecholamine release. Thus, Nav1.3/Nav1.7 channel availability sets the AP shape, burst-firing initiation and regulates catecholamine secretion in MCCs. Nav channel inactivation becomes important during periods of high activity, mimicking stress responses.
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