SK channels in excitability, pacemaking and synaptic integration

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Small conductance calcium-activated potassium channels link elevations of intracellular calcium ions to membrane potential, exerting a hyperpolarizing influence when activated. The consequences of SK channel activity have been revealed by the specific blocker apamin, a peptide toxin from honeybee venom. Recent studies have revealed unexpected roles for SK channels in fine-tuning intrinsic cell firing properties and in responsiveness to synaptic input. They have also identified specific roles for different SK channel subtypes. A host of Ca^{2+} sources, including distinct subtypes of voltage-dependent calcium channels, intracellular Ca^{2+} stores and Ca^{2+}-permeable ionotropic neurotransmitter receptors, activate SK channels. The macromolecular complex in which the Ca^{2+} source, SK channels and various modulators are assembled determines the kinetics and consequences of SK channel activation.

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Introduction

Small conductance calcium-activated potassium (SK) channels are voltage-independent and activated solely by intracellular Ca^{2+}. Three different genes express SK channel subunits in overlapping but distinct patterns in the mammalian brain (SK1, SK2, and SK3), whereas a fourth member of the family, IK1 (SK4), is restricted to peripheral tissues and is not covered in this review. Functional SK channels are heteromeric complexes with constitutively bound calmodulin (CaM); channel opening occurs in response to Ca^{2+} binding to CaM. Importantly, native and cloned SK channels are the only known targets for the bee venom toxin apamin, which blocks the channels with high affinity (K_D values ranging from ~50pM to ~25nM, depending on subunit composition), and it is very likely that the neuronal and behavioral effects of apamin can be attributed to SK channel blockade [1].

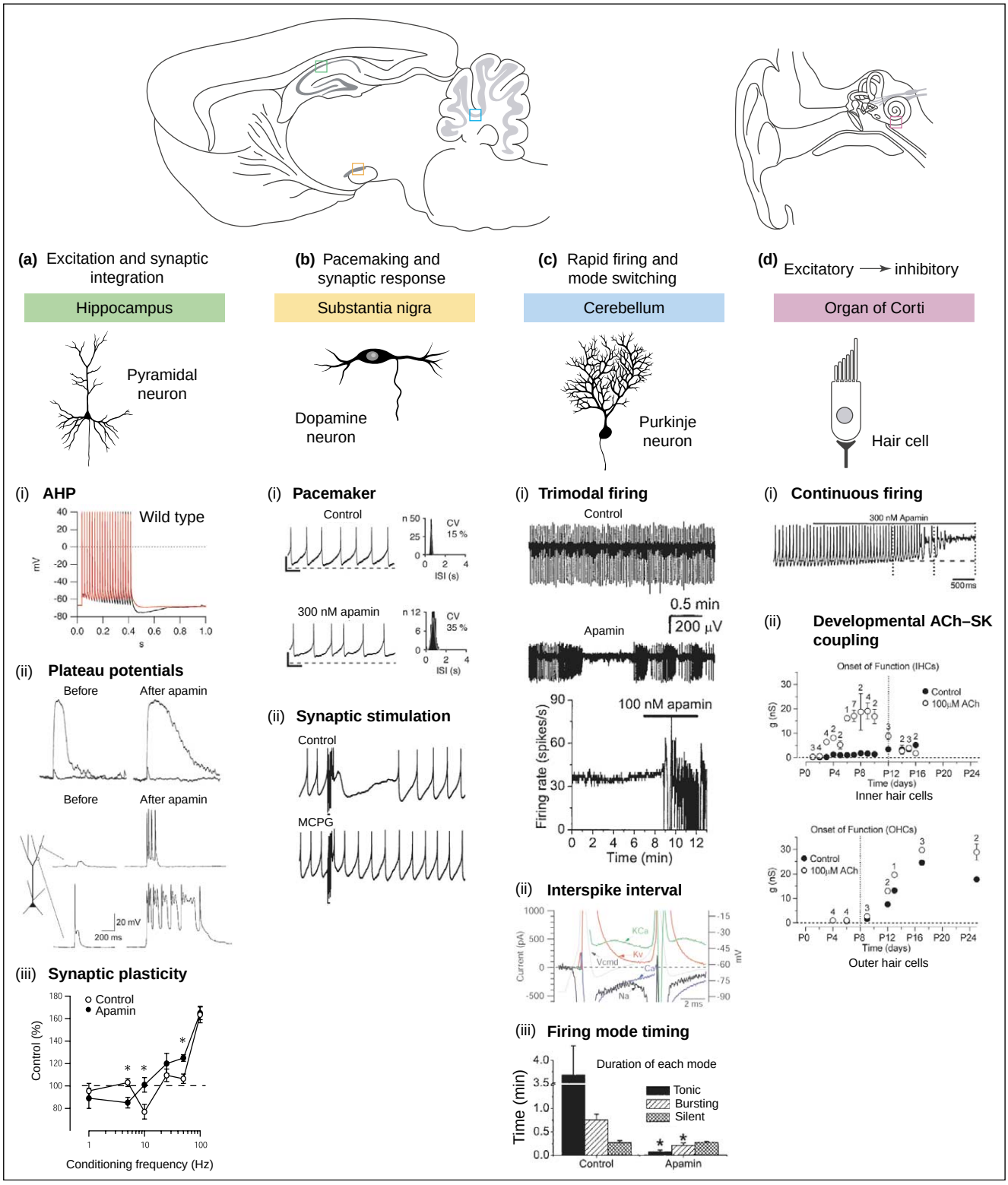
In many neurons, SK channels have a fundamental role in influencing neuronal excitability. SK channels are activated by the transient elevation of intracellular Ca^{2+} that occurs during an action potential, and their activity contributes to a prolonged afterhyperpolarization (AHP) during which the return to baseline reflects the decay of intracellular Ca^{2+} levels.

In the past several years the availability of clones for all four of the SK channels [2–4] has provided not only detailed insights into the biophysical profile of channel gating but also nucleic acid and antibody probes for determination of cellular and subcellular localizations, microdomain organization and developmental profiles. Intensive studies have revealed unexpected roles for SK channels in defining intrinsic cell firing properties, regulating local dendritic Ca^{2+} transients and affecting synaptic plasticity.

Different neuronal populations have exploited the SK-mediated link between elevated Ca^{2+} and membrane potential in specific ways. The emerging theme is that physiological variations are accomplished by the composition of the SK channel molecular neighborhood, the microdomain, in which different Ca^{2+} sources serve to activate SK channels. These macromolecular complexes might include the Ca^{2+} source in addition to modulatory proteins, and the explicit spatial dimensions endow the kinetics of SK channel effects as well as enabling rapid modulation.

At least four models of SK channel function in different cell types in the CNS can be drawn from recent work. First, in cells such as hippocampal and cortical pyramidal neurons, which are essentially silent in the absence of synaptic input, increased intracellular Ca^{2+} during synaptic stimulation or action potential firing activates SK channels. Distinct subcellular populations of channels dampen membrane excitability, contribute to dendritic integration and modulate the induction of synaptic plasticity. Second, in tonically firing cells such as ventral midbrain dopamine neurons, SK channels participate in pacemaking by decreasing inter-spike variability and engendering precise tonic firing that responds bi-directionally to synaptic input. Third, in cells that intrinsically fire at high frequencies, such as cerebellar Purkinje neurons, SK channel activity might be necessary for continued firing and modulation of SK channel activity might effect the normally rhythmic firing behavior.

Figure 1



Four models of SK channel function. Schematic representation of a rat brain and a human ear showing the different regions and cell types exemplifying each of the four models of SK channel function. **(a)** Hippocampus. **(i)** AHP: CA1 pyramidal neuron whole cell current clamp recording. Twenty action potentials were elicited at 50 Hz in control (black) or apamin (red, 100 nM) bath solutions. The control trace shows the development of an interspike AHP and a post-tetanus AHP that are blocked by apamin (JP Adelman, unpublished). **(ii)** Plateau potentials: (Upper)