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Research Report

Single mechanically-gated cation channel currents can trigger action potentials in neocortical and hippocampal pyramidal neurons

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ABSTRACT

The mammalian brain is a mechanosensitive organ that responds to different mechanical forces ranging from intrinsic forces implicated in brain morphogenesis to extrinsic forces that can cause concussion and traumatic brain injury. However, little is known of the mechanosensors that transduce these forces. In this study we use cell-attached patch recording to measure single mechanically-gated (MG) channel currents and their affects on spike activity in identified neurons in neonatal mouse brain slices. We demonstrate that both neocortical and hippocampal pyramidal neurons express stretch-activated MG cation channels that are activated by suctions of ~25 mm Hg, have a single channel conductance for inward current of 50–70 pS and show weak selectivity for alkali metal cations (i.e., $Na^+ < K^+ < Cs^+$). Significantly, single MG channel currents activated on the soma trigger spiking/action potentials in both neocortical and hippocampal pyramidal neurons. Not all neuron types studied here expressed MG channel currents. In particular, locus coeruleus and cerebellar Purkinje neurons showed no detectable MG channel activity. Moreover their robust rhythmic spike activity was resistant to mechanical modulation. Our observation that a single MG channel current can trigger spiking predicates the need for reassessment of the long held view that the impulse output of central neurons depends only upon their intrinsic voltage-gated channels and/or their integrated synaptic input.

1. Introduction

The mammalian brain is generally viewed as an electrochemical organ that carries out its major function of rapid signaling via a variety of voltage-gated and transmitter-gated membrane ion channels. However, it is also well recognized that intrinsic mechanical forces play a role in normal brain development (Franze, 2013) and that extrinsic mechanical

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forces can dramatically alter brain function. In particular, during development axonal tension within the cortical white matter (Van Essen, 1997) and compressive forces within the expanding gray matter (Bayly et al., 2014) have both been implicated in the mechanical folding of the primate neocortex that ensures the compactness of cortical circuitry.

Although the mammalian brain is well protected by a hard skull, multilayered meninges and its neutral buoyant suspension within the cerebrospinal fluid, external mechanical forces (e.g., from direct blows to the head, rapid accelerations/decelerations or high pressure blast waves) can still produce concussion and traumatic brain injury (TBI) with symptoms ranging from rapid, brief loss of consciousness to severe memory, cognitive and motor deficits and progressive neurodegeneration (Glatz, 2004). On the other hand, low intensity transcranial focused ultrasound has recently been used to non-invasively stimulate neocortical neural circuits within living animals and has therapeutic potential (Tufail et al., 2010). Together these results indicate that the brain is a mechanosensitive organ capable of transducing different mechanical forces into a variety of responses (Tyler, 2012). However, little is known of the underlying mechanosensitive mechanisms that transduce these forces.

One interesting class of mechanotransducer is the stretch-activated mechanically-gated (MG) channel that can be experimentally activated at the single molecule level by suction applied to the membrane patch tightly sealed in the tip of patch recording pipette (Hamill et al., 1981; Guharay and Sachs, 1984) or by lipophilic molecules, including specific lipid 2nd messengers (Hardie and Franze, 2012) and various psychotropic drugs (Martinac et al., 1990; Franks and Honore, 2004; Kennard et al., 2005) that gate MG channels by altering lipid bilayer mechanics. Although several types of membrane proteins that form MG channels (e.g., TREK, TMC, PIEZO, and TRPV) have been shown to be expressed in the mammalian brain at the transcript and/or protein level (Fink et al., 1996; Keresztes et al., 2003; Coste et al., 2010; Lee and Choe, 2014) there exists little information on the functional expression of MG channels and their effects on neuronal properties. In this study we use cell-attached patch clamp recording from neonatal mouse brain slices to examine the mechanosensitivity of identified neurons and the effects of mechanical stimulation on spike activity. Our results show for the first time that stretch-activated MG cation channels are powerful modulators of spike output in the principal neurons of the mammalian brain.

2. Results

Cell-attached patch recordings were made from over 100 neurons identified in selected regions of neonatal mouse

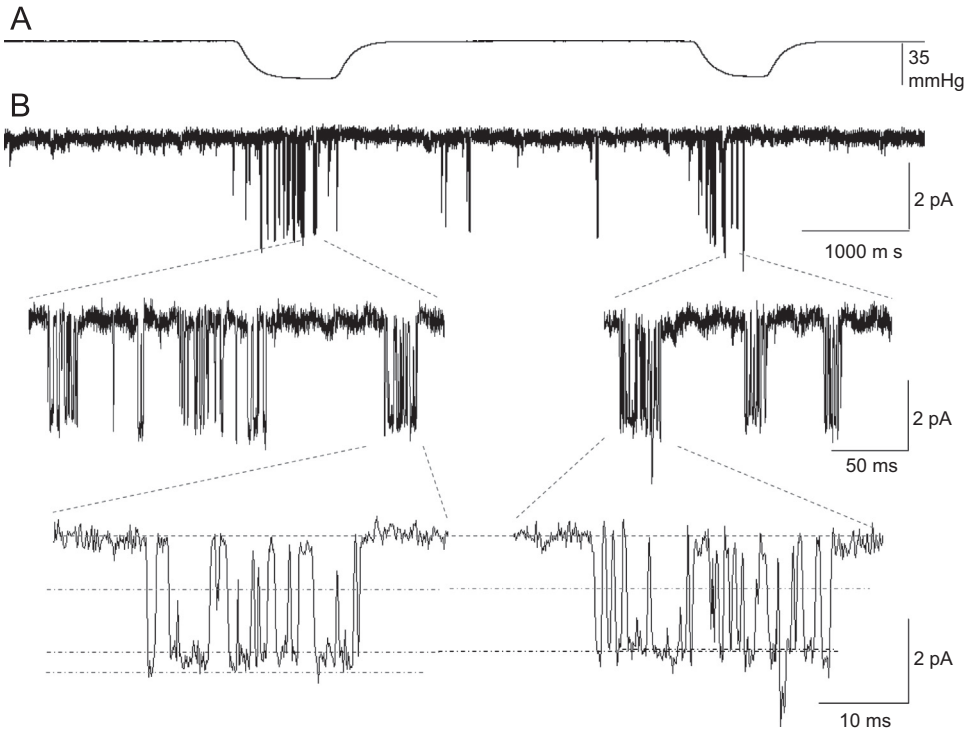

Fig. 1 – MG channel current kinetics measured in cell-attached patches on neocortical pyramidal neurons. A: The pressure waveform of consecutive suction pulses applied to the patch pipette B: The upper trace shows the continuous membrane patch current during the suction pulses and the lower traces show the "bursts" of current events with progressively expanded time scales. Note the "spontaneous" current events that occurred in between the suction pulses. The broken lines indicate smaller and larger current events in addition to the main unitary current events occurring within a single burst. Pipette potential +45 mV, with an estimated membrane potential of −55 mV recorded with 120 mM NaCl pipette solution, postnatal day 10.