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Inhibition Dominates the Early Phase of Up-States in the Basolateral Amygdala

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Windels F, Crane JW, Sah P. Inhibition dominates the early phase of up-states in the basolateral amygdala. *J Neurophysiol* 104: 3433–3438, 2010. First published October 20, 2010; doi:10.1152/jn.00531.2010. Slow oscillations (<1 Hz) in neural activity occur during sleep and quiet wakefulness in both animals and humans. Single-cell recordings in cortical neurons have shown that these oscillations are driven by a combination of excitatory and inhibitory synaptic inputs. During up-states, although the ratio between them varies between cells, excitation and inhibition follow similar time courses. Neurons in the basolateral amygdala (BLA) also show slow oscillations between the resting membrane potential (down-state) and depolarized potentials (up-states). Delivery of footshock during the down-state fully reproduces up-states in these cells. Here we report that up-states in BLA principal neurons up-states begin with an excitatory drive that is rapidly (within ~50 ms) overwhelmed by inhibitory input. This excess of inhibitory drive is short lasting (300–400 ms), after which up-states are maintained by a tight balance between excitation and inhibition. This initial large inhibitory input restricts action potential generation and reduces the firing frequency of these cells. These results indicate that, in contrast to cortical neurons, up-states in BLA neurons show an initial period of strong cortically driven feed-forward inhibition. For the remainder of the up-state, feedback inhibition then acts to balance excitatory input.

INTRODUCTION

Spontaneous oscillations in neural activity over a wide range of frequencies are a common feature of the mammalian brain (Buzsáki 2006; Steriade 1997). These oscillations have been linked to memory formation and consolidation, spatial navigation, and binding of disparate sensory information (Singer and Gray 1995). Of these, the low-frequency (<1 Hz), slow oscillation (Steriade et al. 1993b,c) is seen most prominently during slow-wave sleep and certain forms of anesthesia (Petersen et al. 2003; Steriade et al. 1993b), as well as in acute brain slices maintained in vitro (MacLean et al. 2005; Sanchez-Vives and McCormick 2000; Watson et al. 2008). At the single-cell level, these slow oscillations are seen as spontaneous fluctuations in membrane potential characterized by two phases: down-states, during which the membrane potential is near the resting membrane potential, and up-states, during which neurons depolarize to near spike threshold and may be accompanied by action potentials (Cowan and Wilson 1994; Petersen et al. 2003; Steriade et al. 1993c; Wilson and Kawaguchi 1996).

In the basolateral amygdala (BLA), extracellular field recordings have shown a variety of oscillatory states (Pare et al.

2002): slow oscillations are characteristically seen during slow-wave sleep and anesthesia (Collins et al. 2001; Pare and Gaudreau 1996), whereas higher frequency oscillations in the theta range are present during paradoxical sleep and emotional arousal (Pape et al. 2005; Paré and Collins 2000; Seidenbecher et al. 2003). Amygdala-dependent learning leads to synchronization of oscillatory activity within the amygdala (Pare et al. 2002; Seidenbecher et al. 2003). Single cells recordings have shown that principal neurons of the BLA display a slow oscillation in their membrane potential, moving from periods near the resting membrane potential (down-states) to periods at depolarized membrane potentials (up-states) (Crane et al. 2009).

In cortical neurons, up-states are synaptically driven where both excitatory and inhibitory inputs activate and inactivate with a similar trajectory, maintaining a balanced ratio during the up-state (Sanchez-Vives and McCormick 2000; Shu et al. 2003). In BLA neurons, oscillatory activity is also synaptically driven (Crane et al. 2009); however, the excitatory and inhibitory components of up-states remain to be determined. Here we show that excitation and inhibition in up-states of BLA principal neurons in vivo are not as tightly balanced as in the cortex, being characterized by a dominant inhibitory drive early in the up-state.

METHODS

Data were obtained from Wistar rats (P16–P23; 45 ± 10 g). Animals were housed under standard laboratory conditions with a 12-h light/dark cycle (lights on at 0600 hours), and food and water were available ad libitum. In all procedures, the care and experimental use of animals was in accordance with protocols approved by the University of Queensland Animal Ethics Committee.

Surgery

Animals were anesthetized with urethane (2 g/kg, ip). Once a sufficient level of anesthesia was obtained, animals were mounted in a stereotaxic frame, and their body temperature maintained at 37°C. Following exposure of the skull surface, a hole was drilled unilaterally at coordinates corresponding to the location of the left BLA (2.5–2.6 mm posterior and 4.3 mm lateral to midline), and the dura was carefully retracted. Another hole was drilled on the contralateral side of the skull to allow a reference electrode to be placed on the cortical surface. Footshocks (5–8 mA, 1 ms) were delivered via two 25-gauge needles connected to an isolated current generator (Digitimer) and inserted into the footpad contralateral to the side of the BLA recording (i.e., the right footpad).

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Electrophysiology

Recording pipettes (shank length of 7.5 mm) were fabricated from borosilicate glass using a Sutter P-87, 3 stage pipette puller. For voltage-clamp recordings, the internal solution used was (in mM) 120 CsMeSO₄, 20 TEACl, 10 HEPES, 2 Mg₂ATP, 0.3 Na₃GTP, 0.1 spermine, 10 phosphocreatine, 5 EGTA, 2 CsBAPTA, 5 QX314, and 0.3% neurobiotin; pH 7.3; osmolarity 310 mOsm. For control current-clamp recordings, pipettes were filled with the following internal solution (in mM): 135 KMeSO₄, 7 NaCl, 10 HEPES, 2 Mg₂ATP, 0.3 Na₃GTP, 0.3 EGTA, and 0.3% neurobiotin (pH 7.3; osmolarity, 290–300 mOsm). For high-chloride current-clamp recordings, pipettes were filled with (in mM) 143 KCl, 7 NaCl, 10 HEPES, 2 Mg₂ATP, 0.3 Na₃GTP, 0.3 EGTA, and 0.3% neurobiotin (pH 7.3; osmolarity, 290–300 mOsm). Pipettes had a series resistance of 5–10 MΩ on fabrication and varied between 20 and 50 MΩ during recordings. Recordings with series resistances higher than this were discarded from the final analysis. Signals were amplified using either a Multiclamp 700B or Axopatch 1D (Molecular Devices), filtered at 5 kHz, and digitized at 10 kHz using an Instrutech ITC-18 board. Data acquisition and subsequent analysis were performed using Axograph X (V1.0.8, Axograph scientific). After completion of the recording,

animals were *trans*-cardially perfused with 2% sodium nitrite solution (in 0.1 M phosphate buffer, pH 7.4), followed by 50 ml of 4% formaldehyde (in 0.1 M phosphate buffer, pH 7.4). Brains were removed and postfixed overnight in 4% formaldehyde at 4°C. Serial, coronal forebrain (100 μm) sections were cut using a freezing microtome and processed using DAB-based immunohistochemistry to recover the recorded cell. All cells were confirmed to be pyramidal neurons in the basolateral amygdala (Crane et al. 2009).

Data analysis

Average traces ($n = 8–10$) of footshock-induced currents occurring at -50 mV (excitatory current) and $+20$ mV (inhibitory current) were converted into plots of conductance. Based on the components of our internal solution and accepted values of the concentration of ions within the extracellular fluid, the estimated driving force for excitatory currents was ~ 50 mV, and the estimated driving force for inhibitory currents was ~ 70 mV. Values for excitatory (G_e) and inhibitory (G_i) conductances were calculated from $G_{i/e} = I_{i/e} / (V_m - E_o)$, where G is the conductance, $I_{i/e}$ is the current, and E_o is the reversal potentials. Conductance was plotted with respect to time. The latency to the

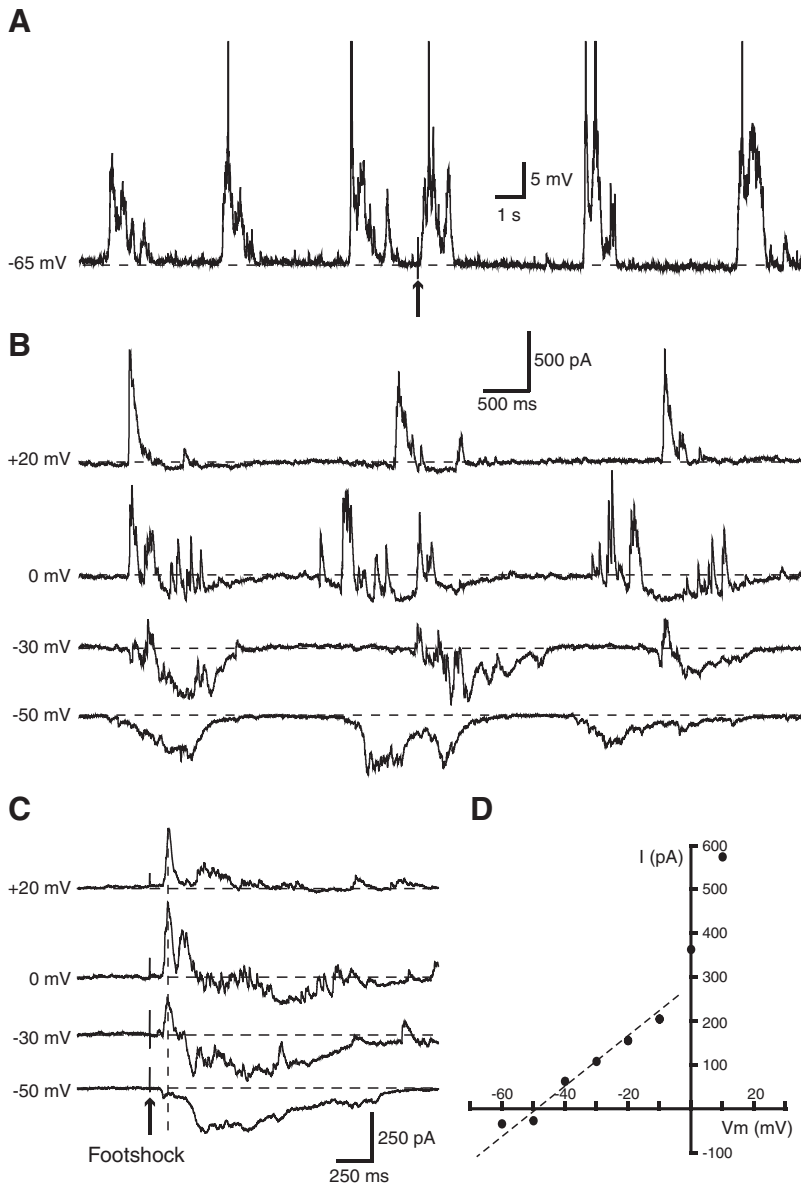


FIG. 1. Up-states in basolateral amygdala principal neurons are characterized by an early period of strong inhibition. *A*: current-clamp recording from a principal neuron *in vivo* shows sustained slow oscillations. Delivery of a footshock (arrow) in the down-state causes an all-or-none transition into an up-state similar to spontaneously occurring up-states. *B*: voltage-clamp recordings using a cesium-based internal solution of spontaneous up-states in a principal neuron voltage clamped at the indicated membrane potentials. Depolarization shows an early, short lasting outward current. *C*: average traces of footshock-induced (arrow) up-states ($n = 10–15$ traces) recorded over a range of membrane potentials. With membrane depolarization, an early short lasting current is apparent, as seen in spontaneous up-states. *D*: current-voltage relationship of the early component for the cell shown in *C*, with peak currents measured at the dotted line in *C*. The dotted line is the linear regression fit to the data between -60 and 0 mV and gives a reversal potential of -47 mV.

up-state onset was measured as the time from the stimulus artifact to when the inward current attained 5% of the initial peak. All statistical comparisons were made using Student's *t*-test, and results are presented as the means \pm SE.

RESULTS

In anesthetized animals, neurons in the BLA show sustained slow oscillations in membrane potential with delivery of a single footshock during the down-state evoking an all-or-none transition into an up-state (Fig. 1A) and entraining the oscillatory phase (Crane et al. 2009). These oscillations are thought to be driven by extra-amygdalar, presumed cortical, synaptic inputs (Crane et al. 2009). To determine the contribution of excitatory and inhibitory conductances to the up-state, neurons were voltage clamped with a cesium-based internal solution containing QX314 to block intrinsic sodium, potassium, and some other voltage-dependent channels (see METHODS). Under these conditions, at a holding potential of -50 mV (near the estimated chloride equilibrium potential), up-states were detected as periodic bursts of inward-current (Fig. 1B). Depolarization of the neuron showed short bursts of outward currents that appeared to be predominantly located at the start of spontaneous up-states (Fig. 1B). At depolarized membrane potentials, the exact onset time of spontaneous up-states, and thus the time course of synaptic inputs driving the up-state, could not be unequivocally established. However, in BLA neurons, footshock-evoked up-states fully reproduce spontaneous up-states (Fig. 1, A and B) (Crane et al. 2009). For example, at a holding potential of -50 mV, footshock-evoked up-states were similar in duration to those occurring spontaneously, with a mean duration of 1.12 ± 0.02 s ($n = 7$), whereas spontaneous up-states had a mean duration of 1.11 ± 0.03 s ($n = 6$, $P = 0.07$). We therefore assume that footshock-evoked up-states are equivalent to spontaneous up-states and examined the time course of up-states evoked by footshocks.

Footshock-evoked up-states recorded over a range of membrane potentials are shown in Fig. 1C. It can be seen that, at depolarized membrane potentials, as with spontaneous up-states (Fig. 1B), there is an early outward current apparent at the start of the up-state that reverses at approximately -50 mV. The mean reversal potential for this early component was -43 ± 3 mV ($n = 5$). The cerebrospinal fluid chloride concentration has been measured to be ~ 150 mM (Hammond and Tritsch 1990), and our internal solution had a chloride concentration of 30 mM, giving a reversal potential of -43 mV for Cl ions. Thus this early current reverses near the predicted chloride equilibrium potential (Fig. 1D), showing the contribution of GABAergic inhibitory synaptic activity to the up-state. The more long-lasting inward current seen is the summated activity of excitatory glutamatergic inputs. At $+20$ mV, near the reversal potential for ionotropic glutamate receptor currents, the outward current has a large early component that decays toward the baseline, showing that there is an initial large transient component of inhibition during the up-state.

To quantify the time course of excitation and inhibition, inward and outward currents (as measured at -50 and $+20$ mV, respectively) were converted to conductance using their predicted reversal potentials (Fig. 2, A and B). Footshock-evoked up-states began with an excitatory component with a

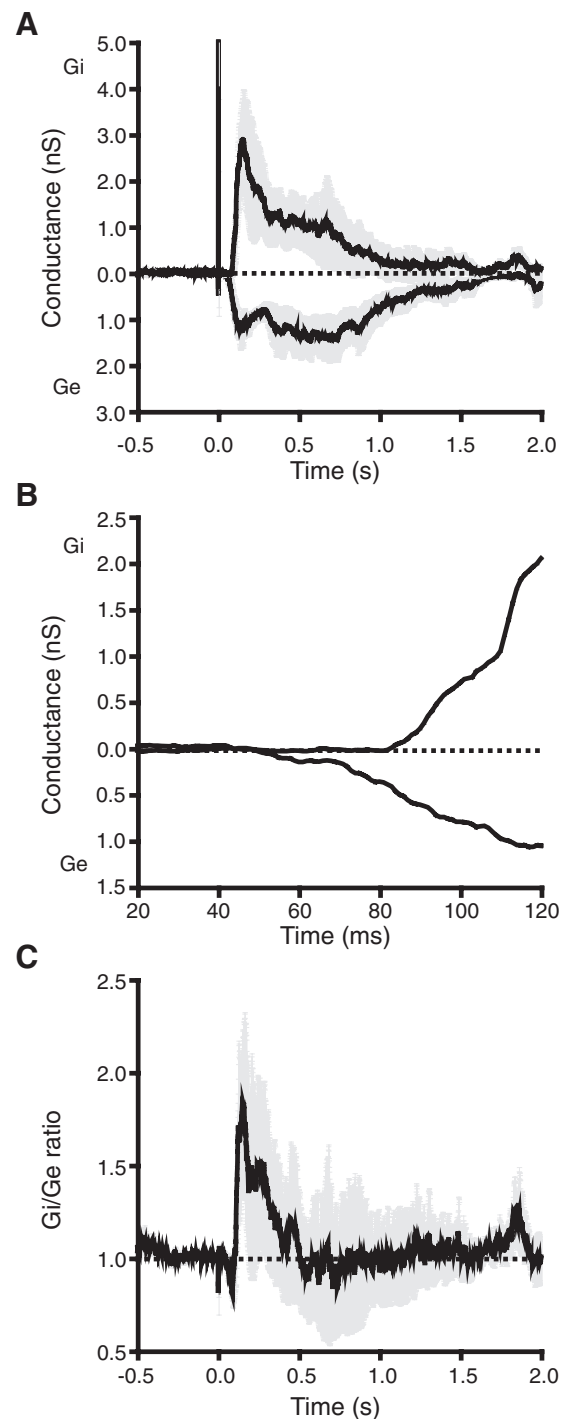


FIG. 2. Inhibition is dominant in the early part of the up-state in the basolateral amygdala. A: mean ($n = 7$ cells) excitatory (G_e) and inhibitory (G_i) drive calculated as conductance change from recordings at -50 (G_e) and $+20$ mV (G_i) ($n = 7$) during footshock-induced up-states. The gray regions plot \pm SD. B: expanded view of the 1st 150 ms of plot in A showing that entry into the up-state begins with excitation that is dominated by inhibition. C: mean G_i/G_e ratio during footshock-induced up-states. Inhibition dominates the early phase but is tightly balanced with excitation during the later phase of the up-state.

latency of 68.5 ± 6.4 ms ($n = 7$) that was rapidly replaced by inhibition (latency = 101 ± 6 ms; $n = 7$). Inhibitory conductance peaked at 148 ± 12 ms ($n = 7$) and was followed by a period during which inhibition and excitation were evenly matched. At its peak, the mean inhibitory conductance was

2,876 ± 1,099 pS, and the mean excitatory conductance was 1,478 ± 433 pS ($n = 7$). To examine the relationship between these two synaptic drives, we calculated the ratio of inhibitory conductance to excitatory conductance during up-states. As can be seen (Fig. 2C), the up-state begins with an excitatory input but is replaced by a dominant inhibitory drive during its early phase. However, this inhibition is short lasting, and excitation and inhibition are tightly balanced during the remainder of the up-state.

To test the functional role of this early dominant inhibition, current-clamp recordings were made with a pipette solution containing high intracellular chloride (143 mM). This internal solution shifts the chloride reversal potential to near 0 mV, such that opening of chloride channels at resting membrane potentials depolarizes the neuron. BLA principal neurons *in vivo* have a low spontaneous firing rate and, consistent with this, up-states were rarely accompanied by action potentials (Figs. 1 and 3), giving a mean firing rate of 0.5 Hz (Crane et al. 2009). In contrast, when loaded with high intracellular chloride, up-states were accompanied by a burst of action potentials (Fig. 3B), with a mean of 6.2 ± 2.7 action potentials per up-state and an overall spike frequency of 2.7 ± 1.2 Hz ($n = 3$). This increase in action potentials was confined to the early part of the up-state, with the average spike frequency during the first 150 ms of the up-state being 5.9 ± 0.8 Hz ($n = 3$) in

chloride-loaded neurons, which is significantly higher ($P < 0.01$) than seen in control conditions (0.93 ± 0.2 Hz, $n = 6$). For comparison, the spike frequency seen 450–600 ms after the onset of the up-state was 5.7 ± 1.6 Hz ($n = 3$), which was not significantly different from that in recordings performed with normal chloride internals (4.1 ± 0.7; $n = 6$; $P = 0.21$). These results are consistent with peak inhibition occurring within the first 150 ms of the up-state and show that inhibition acts early in the up-state as a brake on action potential initiation.

DISCUSSION

Rhythmic slow oscillations in membrane potential are seen in a number of brain regions during some types of anesthesia, as well as slow-wave sleep and periods of quiet wakefulness (Buzsaki and Draguhn 2004; Petersen et al. 2003; Steriade 1997, 2006). In the BLA, oscillatory activity is seen in extracellular field recordings during anesthesia, sleep, and during periods of wakefulness (Collins et al. 2001; Paré and Collins 2000; Pare and Gaudreau 1996; Seidenbecher et al. 2003). Recordings from BLA neurons in anesthetized animals show a slow oscillation in their membrane potential, moving from periods near the resting membrane potential (down-state) to periods at depolarized membrane potentials (up-state) (Crane

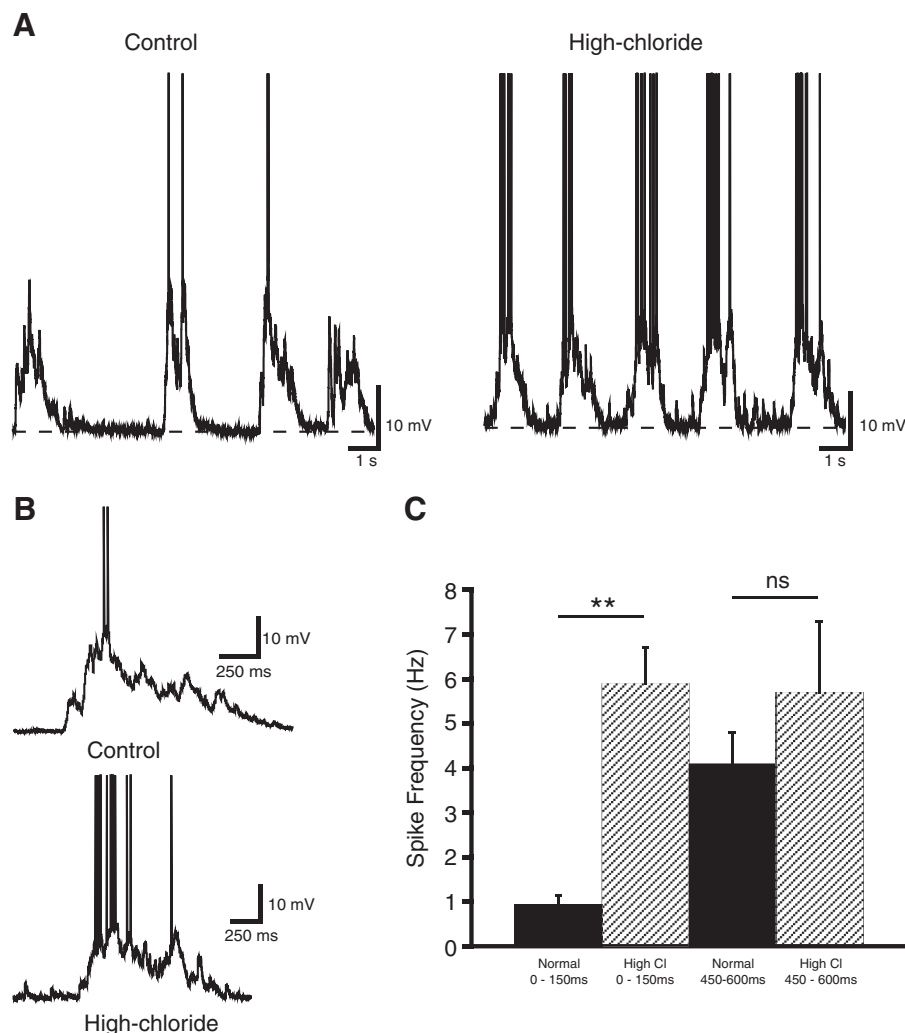


FIG. 3. Early inhibition blocks action potential firing during the early part of the up-state. *A*: spontaneous oscillations recorded using control internal solution (*left*) and an internal solution with high chloride (*right*). Action potentials are more prominent in high chloride internal solutions. *B*: individual up-states recorded under control conditions (top trace) and with chloride loading (bottom trace). *C*: average firing frequency of action potentials during the initial part of the up-state (0–150 ms) and later in the up-state (450–600 ms) measured with normal chloride solution (black bars) and high chloride internals (shaded bars). Significantly higher frequency of action potentials are seen during the early part of the up-state in high-chloride loaded neurons. ** $P < 0.01$.

et al. 2009). In this study, we determined the properties of synaptic inputs that underlie these oscillations. Using whole cell voltage-clamp recordings from principal cells in vivo, we showed that up-states are driven by synaptic input that begins with an excitatory input but is overwhelmed by inhibition after about 50 ms. Inhibition is the dominant synaptic drive in the early part of the up-state but is short lived (~400 ms), being replaced with balanced inhibition and excitation. This dominant inhibition early in the up-state delays action potential firing, thus limiting the overall firing rate of these neurons.

Persistent, spontaneous activity is seen in networks of neurons in cortical and thalamic regions (Steriade 1997; Wilson 2007), with both excitatory and inhibitory neurons displaying similar oscillatory activity (Wilson 2007). Consistent with this, recordings from single neurons show tightly balanced excitatory and inhibitory synaptic input such that inhibitory and excitatory activity covaries during up-states both in vitro (Sanchez-Vives and McCormick 2000; Shu et al. 2003) and in vivo (Haider et al. 2006; Rudolph et al. 2007; Wilson 2007). It is notable that there are clear differences in the absolute ratio of excitation to inhibition with reports where the two conductances are equal during the entire up-state (Shu et al. 2003), whereas in others, inhibition is dominant (Rudolph et al. 2007). The reasons for the difference between these two situations is not known. Using a combination of modeling and single-electrode voltage clamp, this analysis has led to the conclusion that the transition into, and exit from, up-states results from changes in excitatory synaptic input, and the tight balance between excitation and inhibition during the up-state results from local feedback inhibition (Haider et al. 2006; Sanchez-Vives and McCormick 2000; Shu et al. 2003). In our study, whole cell voltage clamping with relatively low-resistance electrodes has allowed us to voltage clamp neurons over a range of membrane potentials to directly assess the contribution of synaptic inputs to the generation of up-states. Although voltage control is not complete, it clearly shows that, whereas oscillations in BLA neurons share some features with those in cortical neurons, there are also clear differences. In cortical neurons, entry into an up-state results from an increase in excitatory drive, and inhibitory input tracks the change in excitation (Haider et al. 2006). In contrast, in the BLA, whereas entry into the up-state is initiated by a rise in excitatory input, it is rapidly overwhelmed by a large, but transient, inhibitory drive. This inhibition then decreases and, as with cortical neurons (Rudolph et al. 2007; Sanchez-Vives and McCormick 2000; Shu et al. 2003), excitatory and inhibitory drive covary during the remainder of the up-state. Moreover, in cortical neurons, entry into the up-state is accompanied by action potentials (Haider et al. 2006), whereas in BLA neurons, the presence of strong inhibition early in the up-state limits action potential generation, resulting in the low action potential discharge during the up-state.

The BLA is a cortical-like structure of which ~80% of the neuronal population are pyramidal-like glutamatergic neurons. The remaining population comprises interneurons with local connections providing both feedforward and feedback inhibition that tightly controls principal neuron activity (Ehrlich et al. 2009; Lang and Pare 1997; Woodruff and Sah 2007). Local inhibition is potent and has a strong inhibitory effect on principal cell firing (Woodruff and Sah 2007). The early onset of strong inhibition, during which time principal neurons show

little activity, suggests that this early inhibition is driven by feedforward local interneurons. Excitatory and inhibitory inputs are balanced during the remainder of the up-state, including the return to the down-state. Because principal neurons are active throughout this later period, the maintained inhibitory activity is likely to result from the activity of local feedback interneurons.

The BLA receives extensive projections from a host of cortical regions (McDonald 1998). Because cortical projections drive up-states in thalamic and striatal neurons (Steriade et al. 1993a; Wilson 1993), it is likely that up-states in BLA neurons are also driven by projections from cortical networks. The similarity of footshock-evoked up-states and spontaneous up-states suggest that footshocks trigger the same cortical networks that are active during spontaneous up-states. Consistent with this is our finding that footshock reset the phase of spontaneous oscillations, and BLA neurons are unresponsive to footshock when delivered during spontaneous up-states (Crane et al. 2009). Our results indicate that, as well as providing the initial excitatory drive to principal neurons of the BLA, cortical inputs also trigger feedforward inhibition via the activation of local interneurons.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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