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Modeling the evolving oscillatory dynamics of the rat locus coeruleus through early infancy

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ABSTRACT

The mammalian locus coeruleus (LC) is a brainstem structure that displays extensive interconnections with numerous brain regions, and in particular plays a prominent role in the regulation of sleep and arousal. Postnatal LC development is known to drastically alter sleep–wake switching behavior through early infancy, and, in rats, exerts its most significant influence from about postnatal day 8 to postnatal day 21 (P8–P21). Physiologically, several dramatic changes are seen in LC functionality through this time period. Prior to P8, LC neurons are extensively coupled via electrical gap junctions and chemical synapses, and the entire LC network exhibits synchronized ~0.3 Hz subthreshold oscillations and spiking. From P8 to P21, the network oscillation frequency rises up to ~3 Hz (at P21) while the amplitude of the network oscillation decreases. Beyond P21, synchronized network oscillations vanish and gap junction coupling is sparse or nonexistent. In this work, we develop a large-scale, biophysically realistic model of the rat LC and we use this model to examine the changing physiology of the LC through the pivotal P8–P21 developmental period. We find that progressive gap junction pruning is sufficient to account for all of the physiological changes observed from P8 to P21.

1. Introduction

The locus coeruleus (LC), a small but important neuronal population within the brainstem, is known to diffusely innervate many key brainstem structures involved in sleep–wake regulation and plays a pivotal role in mammalian sleep and arousal behavior (Andrew Gall et al., 2009), particularly through early postnatal development. Prior experiments in rats have provided several tantalizing clues as to the impact of the LC on the development of sleep–wake cycling from infancy into adulthood. In the early postnatal period (up to postnatal day 8, or P8), rats randomly switch between the sleeping and waking states, spending an exponentially distributed amount of time in a given state prior to a switch. While the mean time spent in each state increases from P2 to P8, the length of sleep or wake bouts remains exponentially distributed (Halász et al., 2004; Lo et al., 2004, 2002; Blumberg et al., 2005; Andrew Gall et al., 2009; Karlsson et al., 2005, 2004; Kleitman and Engelmann, 1953).

Behavioral sleep and wake bouts are correlated with the activity of 'sleep-active' and 'wake-active' populations within the brain that are likely to reciprocally inhibit each other. During a sleep bout, 'sleep-active' neurons fire and

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'wake-active' neurons are quiet, while during a wake bout, 'wake-active' neurons fire and 'sleep-active' neurons are silent. Numerous 'sleep-active' and 'wake-active' populations have been found. Examples of sleep-active populations include the ventrolateral preoptic area (VLPO), medullary inhibitory area (MIA), nucleus pontis oralis (PO), and subcoeruleus (subLC). Wake-active populations are divided into two branches: (1) the thalamic branch (e.g., laterodorsal tegmentum or LDT, pedunculopontine tegmentum or PPT) and (2) the hypothalamic branch (e.g., dorsal raphe nuclei or DR, tuberomamillary nucleus or TMN) (Blumberg et al., 2005; Karlsson et al., 2005; Schwartz and Roth, 2008). In prior work, we investigate switching between neonatal sleep-active and wake-active populations in a simplified two-neuron model (Patel and Joshi, 2014), and we are currently extending these results to mutually inhibitory *populations* of sleep-active and wake-active cells.

From P8 to P21, mean sleep and wake bout lengths continue to increase, and sleep bout times remain exponentially distributed; wake bouts, however, undergo a dramatic *qualitative* change – wake bout lengths gradually develop a heavy-tailed, power law-like distribution (Blumberg et al., 2005). Experimental evidence strongly establishes that the LC is responsible for this qualitative shift in the nature of wake bout times (Berridge et al., 2012; Saper et al., 2001; Takahashi et al., 2010; Aston-Jones and Bloom, 1981; Andrew Gall et al., 2009).

Interestingly, and in step with the remarkable changes in sleep–wake behavior observed through early rat infancy, the rat LC simultaneously exhibits drastic shifts in its physiology and dynamics. In infant rats, experiments have shown that LC neurons display synchronized subthreshold membrane potential oscillations (and synchronized spiking), a tendency which diminishes and finally disappears as the animal ages. Prior to P8, synchronized oscillations have relatively large amplitude (up to 15 mV) and low frequency (~0.3 Hz); the amplitude of synchronized subthreshold oscillations decreases while the frequency increases (up to ~3 Hz) from P8 to P21, after which LC-wide synchrony is rarely observed. Evidence suggests that synchrony across LC neurons in infants may be due to extensive (but weak) electrical coupling via dendro-dendritic gap junctions throughout the entire LC network, while by P21 gap junction connectivity is considerably reduced and insufficient to synchronize LC neurons under normal physiological conditions (Christie, 1997; Coyle and Molliver, 1977; Christie et al., 1989; Travagli et al., 1995; Christie and Jelinek, 1993; Williams and Marshall, 1987; Ishimatsu and Williams, 1996; Groves and Wilson, 1980).

The intriguing concordance between shifting sleep–wake behavior and changing LC physiology during the P8–P21 period suggests that the observed changes in LC functioning may underlie the ability of the LC to modify and influence the physiological behavior of infant sleep-active and wake-active populations. In order to understand the interaction of the LC with brainstem sleep–wake circuitry, a crucial first step is to understand the physiological mechanisms responsible for the evolution of LC dynamics through the early postnatal period.

The rat LC contains ~1500 noradrenergic neurons, and in the infant the probability of electrical coupling between a pair of LC cells is ~0.4. Electrical coupling has been shown to be weak – current injection into cell 1 of a pair of electrically coupled LC cells sufficient to cause a 100 mV depolarization produces only a ~2 mV change in the membrane potential of cell 2. Moreover, if current is injected into cell 1, the time constant of the membrane potential response of cell 1 is ~10 to 20 ms, while the time constant of the potential change in cell 2 (in response to electrical input from cell 1) is ~100 to 300 ms. This suggests that electrical coupling occurs in distal dendrites, and it is important to note that 2 ms action potentials are too fast to be transmitted via the slow gap junctions (Christie, 1997; Christie et al., 1989; Travagli et al., 1995). Synaptic coupling among LC neurons is both excitatory and inhibitory, with coupling properties changing through development. Inhibitory synaptic coupling persists throughout the lifespan of the LC and is mediated via α_2 adrenergic receptors (both presynaptic and postsynaptic), which induce hyperpolarization via opening of K^+ channels, leading to long ~1 to 2 s potential changes (Christie, 1997; Egan et al., 1983; Groves and Wilson, 1980; Ennis and Aston-Jones, 1986). Excitatory synaptic coupling among LC neurons is mediated via α_1 adrenergic receptors transiently in early infancy, while from ~P8 to P21 α_1 receptors vanish and excitatory coupling among LC neurons disappears (Williams and Marshall, 1987). Additionally, evidence indicates that individual LC neurons exhibit intrinsic Ca^{2+} currents and Ca^{2+}-dependent K^+ currents, which may contribute to the subthreshold membrane potential oscillations seen in individual LC neurons, though evidence suggests that synaptic inhibition is sufficient for generating oscillations (Coyle and Molliver, 1977; Ennis and Aston-Jones, 1986). Finally, LC neurons receive synaptic excitatory inputs which induce ~100 ms potential changes from outside the LC network (Cherubini and North, 1988).

In this work, we construct a large-scale computational network model of the rat LC in order to examine the emergence of LC-wide synchrony and subthreshold oscillations, as well as the increase in oscillation frequency and decrease in oscillation amplitude that occurs as the LC ages from P8 to P21, and finally the disappearance of global oscillations and synchrony beyond P21. In the neonatal LC (in which LC neurons are extensively coupled via gap junctions), the network oscillation frequency is ~0.3 Hz (Christie, 1997), corresponding to a period of ~3 s, which is consistent with the long time course of synaptic inhibition induced through α_2 adrenergic receptors. Furthermore, data suggest that intrinsic mechanisms are not essential in generating the post-activation inhibition observed in LC neurons, and that synaptic mechanisms are sufficient (Ennis and Aston-Jones, 1986). Hence, we employ a scaled-down, biophysical model of the neonatal LC consisting of 120 integrate-and-fire neurons coupled via weak dendritic gap junctions and inhibitory α_2 receptors (since spikes are too fast to be transmitted via slow dendritic gap junctions, explicit modeling of the spiking mechanism is unnecessary). We show that our model is capable of reproducing the ~0.3 Hz LC-wide synchronized oscillations observed in the neonatal rat LC, and that progressive gap junction pruning within our model can account for the increasing oscillation frequency and declining oscillation amplitude seen during the P8–P21 period, as well as the disappearance of network coherence after P21. Furthermore,