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The Effects of Anesthesia on Midbrain GABA neurons

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Consciousness has perplexed neuroscientists for decades. What is consciousness and how is it obstructed by anesthesia? Every year doctors expose thousands of people to general anesthesia. Anesthesia does several things, it prevents the perception of pain, renders a patient unconscious, inhibits the formation of memory, and paralyzes the subject; all of which as desired during a medical procedure. The mechanism by which anesthesia accomplishes these many tasks are unknown, including its ability to render a subject unconscious. The goal of this study was to study the effects of anesthesia on γ -aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA) in an attempt to further understand the role that VTA-GABA neurons play in consciousness.

VTA GABA neurons have been implicated in arousal. During behaviors that have been shown to increase an animal's level of arousal, the activity of VTA GABA neurons has been shown to increase (Lee et al., 2001). As an animal sleeps, the activity of VTA GABA neurons slows down and during REM sleep it speeds up (Lee et al., 2001). Moreover, VTA GABA neuron discharge activity synchronizes with gamma electrocortical activity (EEG) during REM sleep(Lee et al., 2001). Thus, there appears to be a connection between an animal's level of arousal and the activity of VTA GABA neurons.

In an effort to further understand how VTA GABA neurons respond during anesthesia we placed electrodes into the VTA of anesthetized Wistar rats. Rats were anesthetized with halothane and stabilized in a stereotaxic apparatus. After a neuron in the VTA was identified to be a GABA neuron, recordings were made as the levels of anesthesia were reduced. As animals underwent the transition from the anesthetized state to wakefulness state neuronal firing increased dramatically, but a strong phasic bursting activity was demonstrated. (Fig 1).

We were very interested in this bursting activity. We sought to identify both the mechanism which induced the bursting and any physiological relevance that this

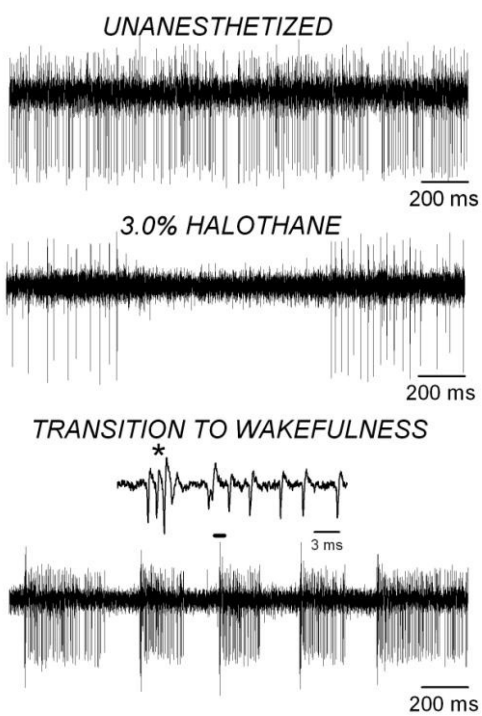

Figure 1.
Top – Neural spike train of an unanesthetized animal. Note the regular activity of VTA GABA neurons during this state.
Middle – Neural spike train of an animal breathing 3.0% Halothane. Note that the firing rate of VTA GABA neurons slows during anesthesia and becomes phasic.
Bottom – Neural spike train of an animal during the transition to wakefulness. Note that the activity of VTA GABA neurons becomes phasic during the transition from anesthesia to wakefulness, but the phasic activity is a higher frequency (i.e., 14 Hz) than that during anesthesia and complex spikes initiate each epoch of discharge activity (see inset for exploded view)

bursting activity might have. An inter-spike-interval-histogram (ISH) was performed to measure the time between the bursts.(Fig 2). The ISH was bimodal, revealing an early peak at spike intervals corresponding to its overall firing rate as well as smaller peak at spike intervals (70msec), a rhythmic frequency of 14Hz. This is particularly interesting because VTA GABA neurons are firing with a beta rhythm during the transition to wakefulness. Beta-rhythm is important because it is largely believed to be the overwhelming rhythm in the brain during the transition from sleeping to consciousness.

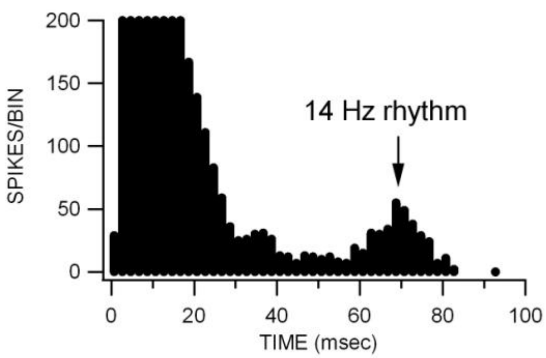

Figure 2.
Inter-spike-interval-histogram (ISIH) of VTA GABA neuron activity during the transition from anesthesia to wakefulness. The bimodal nature of this ISH reflects an overall rhythmic activity of VTA GABA neurons during the transition to wakefulness. Note that there is a late peak around 70 msec that corresponds to about 14 Hz rhythmic activity. The early peak corresponds to intervals whose peak reflects the instantaneous firing rate of VTA GABA neurons.

Further studies must be done that will concretely tie VTA GABA neurons to the regulation of consciousness. VTA GABA neurons are part of a larger network of midbrain tegmentum/reticular formation GABA neurons linked by electrical synapses via gap junctions (Stobbs et al., 2004; Allison et al., 2006; Lassen et al., 2007). We have hypothesized that their synchronous activity leads to cortical arousal. We know some of these GABA neurons in the VTA project to the cortex (Steffensen et al., 1998). However, we don't know where in the cortex they project, or what neurons in the cortex they synapse on to produce their arousal effects. We have recently reported that VTA injections of mu-opioid receptors inhibits VTA GABA neurons(Steffensen et al., 2006) and induces an anesthesia-like state. Recently, others have identified an area in the reticular formation called the mesopontine anesthesia area (Sukhotinsky et al., 2006). We are in a unique position to understand the cellular basis of anesthesia in this area as VTA GABA neurons are part of the mesopontine anesthesia area. This study, albeit simple, has provided enough evidence to merit further research into the link of VTA GABA neurons and consciousness.

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