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Deciphering the Locus Coeruleus-Thalamic Circuit in Anesthetic Emergence

Abstract

As almost 60,000 patients undergo general anesthesia daily in the United States, understanding how anesthetics modulate arousal is important for developing more precise anesthetic care. In particular, volatile and intravenous anesthetics have been shown to modulate the activity of the locus coeruleus (LC)—a predominant source of noradrenergic influence in the brain—to produce unconsciousness, but the mechanism for this remains poorly understood. Norepinephrine infusion into the central medial thalamus can expedite anesthetic emergence, suggesting a potentially significant role of a LC-thalamic circuit in modulating sleep-wake states. Thus, the scientific aims of this career development proposal are to dissect the functional role of the LC-thalamic circuit in anesthetic emergence in a mouse model using a combination of viral tracing, in vivo deep brain imaging, optogenetic manipulation, and transcriptional profiling. First, LC neuronal activity will be visualized at the single-cell level using calcium imaging and its necessity during emergence from isoflurane anesthesia will be determined. Second, the transcriptional profiles of thalamic-projecting LC neurons will be determined during awake and isoflurane-anesthetized states using single-cell combinatorial indexing RNA-sequencing. Together, these studies will support the broader, long-term goal of elucidating the mechanisms by which various anesthetics modulate arousal circuits to shift the balance between sleep-wakefulness. These findings will aide in developing selective anesthetics that minimize cardiovascular side effects and novel drugs to facilitate active anesthetic emergence, and may provide insights into understanding neurological impairments after anesthesia.