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Deconstructing Serotonergic Modulation of Brain State

Abstract

Anesthetic agents exert effects on the brain in part through their action on endogenous neural circuits that modulate sleep. Serotonin neurons powerfully modulate sleep, but the effect of serotonin on sleep is paradoxical. Serotonin promotes sleep in some cases and inhibits sleep in other cases. The paradoxical effect of serotonin on sleep echoes findings in numerous other domains, with serotonin linked to opposing functions like reward and aversion, anxiogenesis and anxiolysis, and increased and decreased locomotion. Progress in understanding the role of serotonin in the mammalian brain is likely to come from two directions. First, converging evidence suggests that the serotonin system is not monolithic, but rather composed of distinct subsets of neurons with separable anatomy and function. This new appreciation of the diversity of serotonin neurons may resolve many paradoxes in serotonin function, as serotonin released from one subset may have different and even opposite effects to that released from another. Second, serotonin affects behavior via modulation of neural activity in downstream brain circuits, but this modulation of neural activity has scarcely been examined. Because serotonergic modulation of neural activity is an intermediate phenotype that mediates effects on behavior, characterizing this modulation is critical to understanding serotonin. In the proposed work, I test the overarching hypothesis that serotonin subsets differentially modulate sleep and neural activity across the brain. To test this hypothesis, I use a viral-genetic strategy to selectively manipulate subsets of neurons while simultaneously characterizing sleep state, other behaviors, and the activity of thousands of neurons across the brain. Given the breadth of brain function regulated by serotonin and wide indications for serotonergic agents, this work has broad relevance to medicine and neuroscience and may define novel biological targets for sleep, anesthesia, and psychopathology.