

## Inducing Emergence Through the Dopaminergic System

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In current clinical practice, emergence from general anesthesia is treated as a passive process dictated by the pharmacokinetics of anesthetic drug elimination. Because the mechanisms underlying anesthetic emergence are poorly understood, related problems such as post-operative delirium and cognitive dysfunction remain significant causes of morbidity in surgical patients.<sup>1-3</sup> No effective methods to treat these problems are currently available.

There are multiple ascending arousal pathways in the brain, and recent findings suggest that many of these neural circuits are involved in emergence from general anesthesia.<sup>4-6</sup> The arousal-promoting neurotransmitters orexin/hypocretin,<sup>7,8</sup> acetylcholine,<sup>9-11</sup> histamine<sup>12,13</sup> and norepinephrine<sup>14,15</sup> have all been implicated in emergence. However, the specific contributions of different arousal pathways to the process of regaining consciousness after general anesthesia remain unclear.

We previously reported that methylphenidate (an inhibitor of the dopamine reuptake transporter) restores conscious behaviors in rats under general anesthesia, and induces EEG changes consistent with arousal.<sup>16,17</sup> We term this active emergence process “reanimation,” distinct from the passive emergence process in current clinical practice. A D1 dopamine receptor agonist also induces reanimation from general anesthesia,<sup>18</sup> providing further evidence for a dopamine-mediated arousal pathway.

Our most recent work using intracranial stimulation shows that an arousal pathway projecting from the ventral tegmental area (VTA) induces reanimation from general anesthesia.<sup>19</sup> Our long-term goal is to provide clinicians with new tools to control the process of emergence. These tools may be useful to treat or obviate emergence-related problems such as delirium and cognitive dysfunction, and may also benefit patients suffering from disorders of consciousness due to brain injury.

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