Brain slices reveal molecular-level secrets of anesthesia

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Video Abstract

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Abstract

The clinical practice of anesthesia is nearly two centuries old. But today, how anesthetics suppress consciousness remains a mystery. Specifically, how do molecular-level drug effects translate into macro-level phenomena? A recent review in the journal *Anesthesiology* looks at how brain slice studies are helping bridge that gap in neuroscience—with recent findings increasingly pointing to the cortex as a critical center of anesthetic action. Anesthesiologists have embraced the acute brain slice method for investigating anesthetic drug effects. Brain slices enable researchers to examine drug actions in isolated, locally connected networks under highly controlled but flexible conditions. Collectively, such studies suggest that both cortical and subcortical regions of the brain, such as the midbrain and thalamus, play important roles in anesthesia, each contributing to both the level of arousal and the content of consciousness. Separating these qualities is difficult, and clear anatomic distinctions may not be possible. For example, microinjection experiments show that targeted drug application to certain subcortical regions can produce or block an anesthesia-like state in the absence of direct effects on the cortex. However, with exogenous manipulation of arousal, the content of consciousness is not easily determined, and no one subcortical site has been identified to be a unifying “anesthesia-sensitive” area. Meanwhile, other studies show that drugs like ketamine make surgical anesthesia possible through actions on cortical neurons without suppression of the thalamus or other subcortical regions. In this instance, information flow between the thalamus and the cortex is not blocked, but the arousal level is not easily measured due to a loss of the content of consciousness. The debate over top-down vs bottom-up mechanisms of the production of anesthesia is not so easily resolved experimentally. However, the recovery from an anesthetized state will depend on the relative anesthetic sensitivity at low concentrations relevant to the clinical situation. For this, the balance of evidence seems to favor cortical over subcortical sensitivity. Acute slices of rodent neocortex suggest that information transfer in and among cortical networks is exquisitely more sensitive to lower concentrations of most anesthetics than the ascending information from subcortical regions controlled by the thalamus. Of course, other factors must always be considered: the type of agent used, the context in which it is used, and the organism receiving it. Monitoring brain activity at this level in human beings will require assays that offer higher resolution than is currently available. Such improvements could help researchers begin to address other outstanding questions. For instance, is the disruption of network activity in the cortex a function of structure or a unique sensitivity of cells in this region to anesthetics? And why is disruption of network activity so powerful in the first place? Further studies on cortical brain slices will undoubtedly help researchers weigh in on these and other issues. And hopefully, with each new discovery, we’ll come one step closer to demystifying the innerworkings of the brain under anesthesia.