

Cellular stress and AMPK activators including metformin and the anesthetic drug propofol promote restoration of human consciousness

The neural mechanisms that give rise to human consciousness have been described as one of the greatest and most profound mysteries in all of modern medicine. The use of general anesthetics to induce loss of consciousness (LOC) in millions of patients each year provides a unique opportunity to determine if various neural circuits play critical roles in the promotion or restoration of consciousness. Many general anesthetics, including propofol, the most widely-used anesthetic to induce and/or maintain general anesthesia in humans, induce LOC in part by potentiating chloride influx through the GABAA receptor, leading to neural inhibition. During the initial period of general anesthesia, known as induction, a bolus dose of an anesthetic drug is administered that leads to LOC. Consciousness is characterized by wakefulness, arousal, cognition, self-awareness, and awareness of one's environment. LOC may be easily assessed by a patient's lack of response to a verbal command from a clinician.

However, an intriguing phenomenon known as paradoxical excitation may also occur after initial administration of an anesthetic drug. When administered at a low dose, nearly every anesthetic drug used clinically may induce behavioral signs of neuronal activation such as eccentric body movements and a transient increase in beta activity (13–25 Hz) on the electroencephalogram (EEG). Consequently, many anesthetics appear to paradoxically excite the brain before inducing unconsciousness. Anesthesiologists and neuroscientists are currently unable to explain how anesthetics are able to induce paradoxical excitation.

AMPK, known as the master regulator of cellular metabolism, increases lifespan and healthspan in several model organisms, is present throughout the mammalian brain (e.g. neurons of the thalamus, hypothalamus, striatum, hippocampus, and cortex), and is activated by cellular stress (i.e. increases in ROS, Ca^{2+} , AMP/ATP ratio, etc.). Increases in ROS and Ca^{2+} play critical roles in neuronal excitation and AMPK is activated by nearly all neurotransmitters that play a critical role in maintaining consciousness (e.g. glutamate, acetylcholine, histamine, orexin-A, dopamine, and norepinephrine) as well as by several anesthetic drugs that are commonly used to induce and/or maintain loss of consciousness in humans (e.g. propofol, sevoflurane, isoflurane, ketamine, dexmedetomidine, and midazolam). Indeed, propofol has been shown to inhibit mitochondrial electron transport chain function and increase ROS levels in human neuroblastoma cells, effects that were enhanced via the addition of the AMPK activator metformin. Metformin also promotes neurogenesis in both the subventricular zone and the dentate gyrus *in vitro* and *in vivo*, potentially enhancing brain repair and recovery from disorders of consciousness (e.g. coma). Various compounds that accelerate emergence from anesthesia, including nicotine, caffeine, forskolin, and carbachol also activate AMPK. Because propofol increases Ca^{2+} levels and activates PBN neurons (critical for maintaining consciousness) just before both loss and return of the righting reflex in rats (analogous to loss and return of consciousness in humans, respectively), propofol is

likely excitatory at low doses and promotes paradoxical excitation and possible facilitation of return of consciousness via cellular stress induction.

Anesthetic-induced paradoxical excitation has also been demonstrated in non-mammalian organisms, with exposure of the nematode *C. elegans* to volatile anesthetics initially resulting in a paradoxical increase in movement, later followed by a progressive lack of coordination, immobility, and ultimately unresponsiveness. Loss of neural AMPK (*aak-2* in *C. elegans*) inhibits movement whereas isoflurane acts as a preconditioning agent in *C. elegans*. Additionally, the anesthetic drug diethyl ether was recently shown to induce a “sedation-like” effect in plants, epitomized by a lack of response to a stimulus that normally induces movement in the Venus flytrap. Preliminary data however demonstrated that the production of ROS by cold (i.e. room-temperature) plasma induced activation and trap closing of the Venus flytrap, suggesting that a common mechanism of cellular stress-induced AMPK activation crosses species boundaries and underlies the phenomenon of anesthetic-induced paradoxical excitation.

Anesthetics and increases in ROS have also been shown to promote seed germination (analogous to paradoxical excitation) and AMPK (SnRK1 in plants), ROS, and Ca^{2+} promotes pollen germination and fertilization in *Arabidopsis thaliana*. Also, although they do not have a nervous system, plants produce nearly all neurotransmitters (i.e. glutamate, acetylcholine, histamine, dopamine, serotonin and norepinephrine) that are critical for maintaining consciousness in humans and biotic and abiotic stressors have been well-described to increase the production and activity of these neurotransmitters in plants. As several neurotransmitters that play key roles in human consciousness also act as preconditioning agents (i.e. glutamate, acetylcholine, histamine, dopamine, and norepinephrine), a common mechanism of cellular stress-induced AMPK activation by neurotransmitters may have been evolutionarily conserved to promote neuronal activation in the human brain.

Lastly, cellular stress and AMPK activation may link human consciousness with seemingly disparate physiological and pathophysiological phenomena, including aging (metformin and AMPK alleviate accelerated aging), human reproduction (stress and AMPK are critical for oocyte maturation and sperm acrosome reaction), gene regulation (e.g. transposable elements, stress beneficially activates “jumping genes” in human cells), plasma medicine (cold plasma induces beneficial effects in cells by increasing ROS), meditation (meditation increases genes in the AMPK signaling pathway in humans), parabiosis (i.e. young blood, young plasma activates AMPK), planarian regeneration (stress and AMPK play crucial roles in regeneration of worm body parts), and stress-induced CRISPR-Cas activation in bacteria (e.g. gene editing technology, various stressors including nutrient starvation and temperature stress activate CRISPR-Cas systems in bacteria).

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