Medical Hypotheses 124 (2019) 42–52

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Cellular stress and AMPK links metformin and diverse compounds with accelerated emergence from anesthesia and potential recovery from disorders of consciousness

Jahahreeh Finley*

Finley BioSciences, Houston, TX 77042-4539, United States

ARTICLE INFO

Keywords:
AMP-activated protein kinase (AMPK)
Consciousness
Anesthesia
Minimally conscious state
Vegetative state
Coma
Propofol
Sevoflurane
Isoflurane
Dexmedetomidine
Ketamine
Midazolam
Long-term potentiation (LTP)
Learning
Memory
Stress
Metformin
Caffeine
Calcium (Ca2+)
Reactive oxygen species (ROS)

ABSTRACT

The neural correlates of consciousness and the mechanisms by which general anesthesia (GA) modulate such correlates to induce loss of consciousness (LOC) has been described as one of the biggest mysteries of modern medicine. Several cellular targets and neural circuits have been identified that play a critical role in LOC induced by GA, including the GABAA receptor and ascending arousal nuclei located in the basal forebrain, hypothalamus, and brain stem. General anesthetics (GAs) including propofol and inhalational agents induce LOC in part by potentiating chloride influx through the GABAA receptor, leading to neural inhibition and LOC. Interestingly, nearly all GAs used clinically may also induce paradoxical excitation, a phenomenon in which GAs promote neuronal excitation at low doses before inducing unconsciousness. Additionally, emergence from GA, a passive process that occurs after anesthetic removal, is associated with lower anesthetic concentrations in the brain compared to doses associated with induction of GA. AMPK, an evolutionarily conserved kinase activated by cellular stress (e.g. increases in calcium [Ca2+] and/or reactive oxygen species [ROS], etc.) increases lifespan and healthspan in several model organisms. AMPK is located throughout the mammalian brain, including in neurons of the thalamus, hypothalamus, and striatum as well as in pyramidal neurons in the hippocampus and cortex. Increases in ROS and Ca2+ play critical roles in neuronal excitation and glutamate, the primary excitatory neurotransmitter in the human brain, activates AMPK in cortical neurons. Nearly every neurotransmitter released from ascending arousal circuits that promote wakefulness, arousal, and consciousness activates AMPK, including acetylcholine, histamine, orexin-A, dopamine, and norepinephrine. Several GAs that are commonly used to induce LOC in human patients also activate AMPK (e.g. propofol, sevoflurane, isoflurane, dexmedetomidine, ketamine, midazolam). Various compounds that accelerate emergence from anesthesia, thus mitigating problematic effects associated with delayed emergence such as delirium, also activate AMPK (e.g. nicotine, caffeine, forskolin, carbachol). GAs and neurotransmitters also act as preconditioning agents and the GABAA receptor inhibitor bicuculline, which reverses propofol anesthesia, also activates AMPK in cortical neurons. We propose the novel hypothesis that cellular stress-induced AMPK activation links wakefulness, arousal, and consciousness with paradoxical excitation and accelerated emergence from anesthesia. Because AMPK activators including metformin and nicotine promote proliferation and differentiation of neural stem cells located in the subventricular zone and the dentate gyrus, AMPK activation may also enhance brain repair and promote potential recovery from disorders of consciousness (i.e. minimally conscious state, vegetative state, coma).

Introduction

One of the greatest and most profound mysteries in all of modern medicine is identification of the neural correlates that underlie human consciousness and the mechanisms through which general anesthesia (GA) induce a loss of consciousness (LOC) [1]. The use of general anesthetics to successfully induce LOC and maintain GA in millions of patients each year provides a unique opportunity to assess and determine if specific neural circuits play critical roles in promoting consciousness [2]. Consciousness is characterized by wakefulness, arousal, cognition, self-awareness, and awareness of one's environment and LOC may be easily assessed by a patient's a lack of response to a verbal command from a clinician [3]. Loss of the righting reflex (LORR) in rodent models in response to general anesthetics has also proven to be

* Address: Finley BioSciences, 9900 Richmond Avenue, Houston, TX 77042-4539, United States.
E-mail address: jfinley4@alumni.jh.edu.

https://doi.org/10.1016/j.mehy.2019.01.014
Received 17 November 2018; Accepted 19 January 2019

an excellent surrogate for LOC in human patients, rendering animal models as powerful investigative tools to study consciousness [3,4].

GA, which has been described as a drug-induced reversible coma, is characterized by unconsciousness, amnesia, akinesia (loss of voluntary movement), and analgesia (loss of response to pain) and typically consists of three periods [3]. During the initial period, known as induction, a bolus dose of an anesthetic drug is administered that leads to LOC as evidenced by a lack of response to an oral command. However, an intriguing phenomenon known as paradoxical excitation may also occur after initial administration of an anesthetic drug [3–5]. When administered at a low dose, nearly every anesthetic induces behavioral signs of neuronal activation such as eccentric body movements and a transient increase in beta activity (13–25 Hz) on the electroencephalogram (EEG) [3,5]. Consequently, many anesthetics appear to paradoxically excite the brain before inducing unconsciousness [3,6]. After induction and LOC, the maintenance period of GA is achieved via a combination of drugs and anesthetics and is associated with a decrease in EEG beta activity (phase 1), an increase and anteriorization of lower frequency alpha (8–12 Hz) and delta (0–4 Hz) activity (phase 2), an EEG activity comprising flat periods interspersed with beta and alpha activity (i.e. burst suppression, phase 3), and an isoelectric EEG (i.e. flat, phase 4) [3,7]. Emergence from GA is a passive process that occurs after the removal of anesthesia, approximates an EEG reversal from maintenance period phases 2 or 3, and is characterized by the return of various physiological processes and responses to verbal commands [3,7,8].

Although a number of structurally diverse compounds are used during GA to induce LOC, the GABAA receptor has been identified as a primary target for several anesthetic drugs, including propofol, sevoflurane, isoflurane, and midazolam [9]. By binding post-synaptically to GABAA receptors located on excitatory pyramidal neurons in the brain (e.g. cortex), anesthetics potentiate GABA-mediated increases in chloride (Cl-) influx through the GABAA receptor, leading to neural inhibition and LOC [3,9]. GABA is the primary inhibitory neurotransmitter within the brain and GABA release from cortical interneurons play an important role in inhibition of excitatory pyramidal neurons and LOC [3,7,9]. The NMDA receptor (NMDAR) located on inhibitory interneurons in the cortex, hippocampus, and limbic system has also been shown to be a primary target for ketamine, an anesthetic drug that functions as an NMDAR antagonist and induces LOC by promoting an increase in uncoordinated neural activity [3,7,9]. An additional cellular target contributing to LOC is the a2-adrenergic receptor found on neurons from the locus ceruleus [10]. a2-adrenergic receptor agonists, including dexmedetomidine, clonidine, and xylazine promote LOC by inhibiting release of norepinephrine in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus [3,10]. As norepinephrine inhibits GABA and galanin release from VLPO neurons, a2 agonist-mediated disinhibition of VLPO neurons contribute to LOC via GABA- and galanin-mediated inhibition of various arousal nuclei in the brain [3,10]. Such nuclei include cholinergic neurons in the lateral dorsal and pedunculopontine tegmental nuclei, histaminergic neurons in the tuberomammillary nucleus, dopaminergic neurons in the ventral periaqueductal gray area, and serotonergic neurons in the dorsal raphe nucleus [3,4,7]. Other arousal nuclei that play important roles in LOC include cholinergic neurons in the basal forebrain, orexinergic neurons in the lateral hypothalamus, dopaminergic neurons in the ventral tegmental area, and glutamatergic neurons in the parabrachial nucleus [3,4,7,11].

AMPK, known as the master regulator of cellular metabolism, is an evolutionarily conserved serine/threonine kinase that increases lifespan and/or healthspan in several model organisms [12,13]. The induction of cellular stress, mediated by increases in the AMP(ADP)/ATP ratio, increases in intracellular reactive oxygen species (ROS), or an increase in intracellular calcium (Ca2+) levels leads to AMPK activation via phosphorylation of the AMPK catalytic α subunit by the upstream kinases liver kinase B1 (LKB1) or Ca2+/calmodulin-dependent protein kinase kinase-β (CaMKKβ or CaMKK2) [12–14]. AMPK activation promotes several cellular processes critical for neuronal function and survival, including mitochondrial oxidative phosphorylation, autophagy, and mitochondrial biogenesis [12,13,15]. Activation of AMPK has also been demonstrated to play a beneficial role in diverse neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's disease [16–18]. Numerous structurally dissimilar compounds induce AMPK activation, including the AMP analog AICAR, the anti-diabetic drug metformin, and several plant-derived and naturally-occurring compounds (e.g. caffeine, forskolin, nicotine, etc.) [19–22].

Hypothesis

We propose the novel hypothesis that cellular stress-induced AMPK activation, mediated by increases in intracellular Ca2+, ROS, and/or an AMP(ADP)/ATP ratio increase, etc. links wakefulness, arousal, and consciousness with paradoxical excitation and accelerated emergence from anesthesia. AMPK is located throughout the brain and in areas that are critical for LOC induced by GA, including neurons of the striatum, thalamus, and hypothalamus as well as in pyramidal neurons located in the hippocampus and cortex. Increases in intracellular Ca2+ and ROS activate AMPK and play important roles in facilitating neuronal excitation and glutamate, the primary excitatory neurotransmitter in the human brain, activates AMPK in cortical neurons. Nearly every neurotransmitter released from ascending arousal nuclei that promote wakefulness, arousal, self-awareness, and consciousness activates AMPK, including acetylcholine, histamine, orexin-A, dopamine, and norepinephrine. Several general anesthetics that are commonly used to promote LOC in human patients also induce paradoxical excitation in low doses and activate AMPK (e.g. propofol, sevoflurane, isoflurane, dexmedetomidine, ketamine, and midazolam). Because lower concentrations of anesthetics are present in the brain during emergence from GA compared to the initial induction phase, it is likely that cellular stress-induced AMPK activation in neurons by excitatory neurotransmitters and low doses of anesthetics represents a common mechanism linking paradoxical excitation with return of consciousness and emergence from GA. Indeed, the GABAA receptor inhibitor bicuculline, which reverses propofol anesthesia, also activates AMPK in cortical neurons. Transient increases in ROS, Ca2+, and AMPK and various neurotransmitters and general anesthetics also act as preconditioning agents, indicating that preconditioning is analogous to paradoxical excitation and is mediated through a common mechanism of AMPK activation. Furthermore, compounds including nicotine, caffeine, forskolin, and carbachol that have recently been shown to accelerate emergence from anesthesia in both animal models and in humans activate AMPK, indicating that restoration of consciousness by structurally distinct compounds may act via AMPK. Moreover, nicotine and the AMPK activator metformin promote proliferation and differentiation of neural stem cells located in the dentate gyrus and the subventricular zone, suggesting that AMPK may also enhance brain repair and promote potential recovery from disorders of consciousness (i.e. minimally conscious state, vegetative state, coma).

Evaluation of the hypothesis

AMPK is present in neurons throughout the brain and is activated by stress and arousal-promoting neurotransmitters

Wakefulness, arousal, cognition, self-awareness, and awareness of one's environment are critical components of consciousness and likely require coordinated communication among neural circuits located throughout the brain. As such, any candidate proteins that are hypothesized to play a central role in restoring and/or maintaining consciousness must also possess a ubiquitous presence in the brain. Culmsee et al. found that the AMPK catalytic α2 subunit was present throughout the adult rat brain, including in neurons of the thalamus,

hypothalamus, and striatum as well as in pyramidal neurons in the hippocampus and cortex [23]. The AMPK activator AICAR protected hippocampal neurons from cell death induced by hypoxia and glucose deprivation whereas antisense oligonucleotide-mediated suppression of AMPK α1 and α2 subunits exacerbated cell death following glucose deprivation and abrogated AICAR-mediated neuronal protection [23]. Pyramidal neurons in the cortex are also primary targets of several anesthetic drugs and the thalamus, striatum, and arousal nuclei in the hypothalamus play critical roles in maintaining consciousness, highlighting the potential importance of AMPK in LOC and emergence from GA [3]. As excitatory cortical pyramidal neurons likely represent key components of the neural correlates of consciousness, pyramidal neurons located in the CA1 region of the hippocampus have also been shown to play a critical role in long-term potentiation (LTP), a form of synaptic plasticity that is widely considered to be the cellular correlate of learning and memory [3,24].

The induction of cellular stress is essential in facilitating hippocampal LTP and AMPK is activated by compounds and methodologies that promote LTP [24]. Similar to activation of excitatory pyramidal neurons in the cortex, induction of hippocampal CA1 LTP is dependent on an increase in the levels of intracellular Ca2+ [25]. Ca2+ and ROS have been shown to engage in a positive feedback mechanism and treatment of rat hippocampal neurons with AMPA and NMDA, ligands for the glutamate receptors AMPAR and NMDAR, increases mitochondrial-derived superoxide generation [26,27].

Treatment of hippocampal slices with a superoxide-generating system induces CA1 LTP, application of a superoxide dismutase (SOD) mimetic (neutralizes ROS) prevents CA1 LTP induced by high frequency stimulation, and overexpression of SOD prevents CA1 LTP in transgenic mice [28–30]. Metformin also has also been shown to activate AMPK in hippocampal CA1 pyramidal neurons, indicating that cellular stress (mediated by ROS, Ca2+, and/or AMP(ADP)/ATP ratio increases) is critical for the induction of hippocampal CA1 LTP [31]. Interestingly, neurons of the thalamus have been shown to release glutamate in the prefrontal cortex and the primary sensory cortices (e.g. visual, auditory, and somatosensory cortices), the NMDAR facilitates LTP of thalamic neurons that synapse onto neurons located in the primary visual cortex, and NMDA activates AMPK in cortical neurons [32,36–38].

Marinangeli et al. recently showed that the AMPK inhibitor compound C severely impaired hippocampal CA1 LTP and significantly reduced the expression of the immediate early genes Arc, Egr1, and cFos after synaptic activation [188]. Compound C also blocked long-term memory formation in mice during an inhibitory avoidance task, indicating that AMPK activation is likely required for LTP, learning, and memory [24,188]. Furthermore, similar to the critical role AMPK plays in facilitating LTP, AMPK is also activated in cortical neurons by glutamate, the primary excitatory neurotransmitter in the human brain, indicating that AMPK activation may also represent a key mechanism within the neural correlates of consciousness [32]. Potassium chloride (KCl), which is widely used to induce neuronal depolarization, also activates AMPK in rat cortical neurons [32]. Chen et al. demonstrated that depolarization and excitation of rat visual cortical neurons with KCl led to a rapid activation of AMPK and a significant increase in ATP production as well as the mRNA expression levels of NRF-2α, PGC-1α, and mtTFA, proteins that play critical roles in regulating and enhancing mitochondrial oxidative phosphorylation and mitochondrial biogenesis [33,34]. AICAR and resveratrol also activated AMPK and increased ATP levels and the expression levels of NRF-2α whereas the AMPK inhibitor compound C blocked KCl- and resveratrol-induced increases in NRF-2α, PGC-1α, mtTFA, and ATP [33]. Metformin was also shown to inhibit respiratory chain complex I activity in rat primary cortical neurons and protect neurons from etoposide-induced cell death, strongly indicating that cellular stress-induced AMPK activation resulting from mild complex I inhibition is neuroprotective in cortical neurons [35].

Moreover, similar to the activation of AMPK in cortical neurons by glutamate, nearly every neurotransmitter released from arousal circuits that promotes wakefulness, arousal, and consciousness activates AMPK, including histamine, dopamine, acetylcholine, norepinephrine, and orexin-A [39–43]. Serotonin also likely activates AMPK as Laporta et al. showed that the serotonin precursor 5-hydroxytryptophan induces AMPK activation *in vivo* in rats [44]. As such, and because potentiation of chloride influx through the GABAA receptor is a primary mechanism by which anesthetics including propofol and sevoflurane promote LOC, it would be expected that GABAA receptor inhibitors that reverse GA would activate AMPK. Indeed, the GABAA receptor antagonist bicuculline reverses propofol anesthesia and activates AMPK in mouse cortical neurons [45,46]. Stimulation of primary mouse cortical neurons with bicuculline (via neuronal dis-inhibition) led to an increase in synaptic activity and a rapid and sustained activation of AMPK mediated by Ca2+ influx through NMDARs and L-type voltage-gated calcium channels [46]. Flumazenil, a GABAA receptor inhibitor that also accelerates emergence from sevoflurane GA in humans, protects myocytes by acting as a preconditioning agent via increasing the levels of ROS, suggesting that flumazenil may promote accelerated emergence from anesthesia partly by activating AMPK [47,48]. Additionally, bicuculline, flumazenil, and the GABAA receptor inhibitors picrotoxin, pentylenetetrazol, and bilobalide ameliorate deficits in memory and hippocampal LTP in mouse models of Alzheimer's disease and Down syndrome (DS) [49–51]. A combination of resveratrol and EGCG (AMPK activators found in various plants) improved neural progenitor cell proliferation in a DS mouse model and treatment of human fibroblasts derived from DS fetuses with metformin reversed mitochondrial defects, suggesting that AMPK activation likely represents a common mechanism through which diverse GABAA receptor antagonists elicit various therapeutic effects [52–54].

As discussed above, GABA and galanin release from VLPO neurons contribute to anesthetic-induced LOC via inhibition of various arousal nuclei associated with wakefulness. Expectedly, VLPO neurons are also active during non-rapid eye movement (NREM) sleep, a phase of physiological sleep that displays EEG patterns similar to sedation induced by dexmedetomidine [3,55]. As similar neural circuits are involved in both sleep and GA, changes in energy metabolism and AMPK activation should also be evident during sleep and wakefulness. Dworak et al. showed that during the initial periods of sleep in rats, ATP levels increase significantly in the frontal cortex and basal forebrain, two areas of the brain that play a critical role in anesthetic-induced LOC [56]. NREM delta activity (0.5–4.5 Hz) was also significantly higher during the initial stages of sleep. Short-term sleep deprivation however attenuated the increases in ATP levels in several brain regions including the frontal cortex and lateral hypothalamus, indicating that short-term sleep deprivation or extended periods of wakefulness represents an endogenous cellular stressor [56]. As increases in the AMP(ADP)/ATP ratio activate AMPK, short-term sleep deprivation also significantly increased AMPK activation in the basal forebrain compared to control animals [56]. Nikonova et al. further confirmed that sleep deprivation increased the mRNA levels of nuclear respiratory factors Nrf1 and Nrf2, mitochondrial electron transport chain complex IV proteins, and phosphorylated/activated AMPK in the mouse cerebral cortex [57]. Short-term sleep deprivation also increases hippocampal neurogenesis in rats and exerts antidepressant effects in humans, indicating that cellular stress-induced AMPK activation likely represents a common mechanism linking learning and memory with wakefulness, arousal, and consciousness [24,58,59].

Moreover, creatine, an amino acid that increases exercise performance, significantly decreases total sleep time and ATP levels in the cerebral cortex and basal forebrain and reduces NREM delta activity in rats [60]. Creatine has also been shown to activate AMPK in rat skeletal muscle cells [61]. Furthermore, treatment of rats with a combination of the anesthetic drugs ketamine and xylazine led to a LORR (i.e. surrogate marker for LOC in humans) and a significant increase in ATP levels in the frontal cortex and basal forebrain that positively correlated with an increase in EEG delta activity, mirroring results obtained during initial

stages of sleep in rats [62]. Xylazine, an analog of the anesthetic clonidine, induces sedation by acting as an agonist of the a2-adrenergic receptor, similar to dexmedetomidine [63]. Curiously, however, both ketamine and clonidine have been shown to induce AMPK activation and xylazine activates AMPK in the rat cerebral cortex, hippocampus, thalamus, and cerebellum [64–66]. As further explained below, nearly every anesthetic used clinically to induce LOC in humans activates AMPK, suggesting that AMPK may promote anesthetic-induced paradoxical excitation and possibly facilitate a restoration of consciousness.

Anesthetics induce paradoxical excitation, activate AMPK, and act as preconditioning agents

Although anesthetic drugs effectively induce LOC at appropriate doses, nearly every general anesthetic used clinically to induce LOC in humans may also induce paradoxical excitation at low doses [3]. As the name implies, paradoxical excitation is a phenomenon in which an anesthetic that is used to promote LOC instead induces behavioral indications of neuronal excitation on initial administration (e.g. eccentric body movements) as well as transient increases in EEG beta activity [3,6]. Intriguingly, healthy adult volunteers also exhibit prominent EEG beta activity just before emergence from general anesthesia and Friedman et al. showed that brain concentrations at the EC_{50} for induction (i.e. LORR) for both halothane and isoflurane are significantly greater than at emergence for both anesthetics in wild-type mice [67,68]. Similarly, estimated propofol concentrations at the EC_{50} for induction were significantly greater than at emergence in human neurosurgical patients [189]. Serum concentrations of propofol were also shown to be higher at loss of responsiveness compared to recovery of responsiveness in human volunteers [190]. Such evidence indicates that a decrease in the concentration of an anesthetic in the brain to a low, stimulatory level after removal of anesthesia may explain the increase in beta activity just before return of consciousness, similar to low-dose anesthetic-induced paradoxical excitation.

Anesthetic-induced paradoxical excitation has also been demonstrated in non-mammalian organisms, suggesting that a common mechanism underlying this phenomenon may cross species boundaries. Exposure of the nematode *C. elegans* to volatile anesthetics for example initially results in a paradoxical increase in movement, later followed by a progressive lack of coordination, immobility, and ultimately unresponsiveness. Removal of the anesthetic however quickly leads to a return of motion [69,70]. Loss of neural AMPK (aak-2 in *C. elegans*) inhibits movement whereas isoflurane acts as a preconditioning agent in *C. elegans* [71,72]. 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 [73]. 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 [191]. Indeed, anesthetics and increases in ROS have also been shown to promote seed germination (analogous to paradoxical excitation) and AMPK (SnRK1 in plants), ROS, and Ca2+ promotes pollen germination and fertilization in *Arabidopsis thaliana*, indicating that cellular stress-induced AMPK activation likely facilitates neuronal activation and paradoxical excitation in humans [74–77].

As noted above, the anesthetic clonidine activates AMPK *in vivo* in mice and the clonidine analog xylazine activates AMPK throughout the rat brain *in vivo*, suggesting that AMPK activation may be a common mechanism shared by low-dose anesthetic administration [64,66]. Propofol, the most widely-used anesthetic to induce and/or maintain general anesthesia in humans, was recently shown to induce AMPK activation in both mouse and human cells. Chen et al. showed that exposure of C2C12 mouse myoblast cells to propofol led to an increase in cytoplasmic Ca2+ concentrations facilitated by IP3R-mediated Ca2+ release from the ER [78]. Propofol also significantly increased intracellular ROS production which was partially mitigated by the ER stress inhibitor TUDCA, indicating that intracellular Ca2+ increases likely potentiate increases in ROS production [26,78]. Importantly, propofol enhanced cellular viability and autophagy, induced phosphorylation and activation of AMPK, but inhibited activation of mTOR (a serine/threonine kinase that inhibits autophagy) [78]. Similar results were also observed in human cells. Treatment of HeLa human cervical cancer cells with propofol stimulated ER stress and increased intracellular Ca2+ levels and autophagosome accumulation [79]. Propofol also activated AMPK and inhibited mTOR whereas ER stress and the expression of autophagy markers was abrogated by TUDCA, indicating that propofol promotes AMPK activation in various cell types via the induction of cellular stress [79].

Additionally, clinically relevant concentrations of propofol increases differentiation of rat hippocampal-derived neural precursor/stem cells and propofol elevates cytoplasmic Ca2+ concentrations and promotes proliferation of adult rat neural stem cells [80,81]. Propofol in clinically relevant concentrations has also been shown to stimulate human cortical neural progenitor cell proliferation and differentiation into a neuronal cell fate via IP3R-mediated Ca2+ release from the ER [82]. Propofol also improved cellular proliferation and exerted a neuroprotective effect in human neuroblastoma SH-SY5Y cells [83]. Intriguingly, propofol has been shown to stimulate the receptors TRPA1 and TRPV1, increase intracellular Ca2+ levels, and paradoxically activate nociceptive sensory neurons, contributing to the well-documented injection-site pain on initial propofol administration [84]. AITC and capsaicin, agonists for TRPA1 and TRPV1, respectively, both activate AMPK, providing further evidence that low-dose anesthetic-induced AMPK activation likely plays a critical role in neuronal activation, paradoxical excitation, and consciousness [85,86].

Other structurally diverse anesthetic drugs have also been shown to induce AMPK activation. The volatile anesthetic sevoflurane demonstrated cardioprotective effects against ischemia/reperfusion (I/R) injury in isolated rat hearts via ROS-induced AMPK activation [87]. Sevoflurane preconditioning increased ROS and activated AMPK *in vivo* in rats and significantly reduced infarct size following myocardial I/R in an AMPK-dependent manner [88]. Sevoflurane also induced an IP3R-mediated increase in intracellular Ca2+ levels in a cholinergic cell line and enhanced aversive memory formation in rats at low doses [89,90]. Preconditioning of mice with the inhaled anesthetic isoflurane attenuated liver IR injury in an AMPK-dependent manner and low doses of isoflurane promote proliferation and differentiation of human cortical neural progenitor cells via IP3R-mediated increases in intracellular Ca2+ levels, similar to propofol and sevoflurane [91,92]. The dissociative anesthetic ketamine was shown to activate AMPK in the rat hippocampus *in vivo* and the rapid antidepressant effect of ketamine was attenuated by an AMPK antagonist [93]. Ketamine also activates Ca2+ channels in rats to induce antidepressant effects, increases ROS in mouse brain, enhances hippocampal LTP at CA3-CA1 synapses in adult rats, and reduces symptoms of depression and suicidality in human patients [94–97]. Dexmedetomidine inhibits cerebral I/R-induced neuroinflammation in rats via AMPK activation, midazolam activates AMPK *in vivo* in rats, and thiopental (a barbiturate anesthetic) ameliorates hypoxic cell damage and activates AMPK in human neuronal SK-N-SH cells [98–100]. Additionally, the local anesthetic lidocaine suppresses neuroinflammation and alleviates morphine tolerance via AMPK activation in the mouse spinal cord, indicating that AMPK activation represents a common mechanism linking the beneficial effects associated with low-dose anesthetic administration [101].

Several general anesthetics also function as preconditioning agents for a variety of cell types. Preconditioning refers to the exposure of a cell or an organism to a mild or sublethal stressor that leads to an adaptive response and protection against a subsequent and potentially lethal application of the same or a similar stressor [102,103]. Numerous compounds and methodologies exert preconditioning effects or act as preconditioning agents, including fasting, exercise, hydrogen sulfide, and hydrogen peroxide [102,103]. Because the induction of cellular

stress plays a critical role in neuronal activation and paradoxical excitation and because AMPK is present in neurons throughout the brain, it is likely that a primary mechanism through which general anesthetics function as preconditioning agents is via cellular stress-induced AMPK activation. Temperature preconditioning of rat myocytes leads to a cardioprotective effect that is dependent on increases in mitochondrial ROS production and the ROS scavenger NAC inhibits hypoxic preconditioning-induced improvement of human adipose stroma/stem cell angiogenic capacities [104,105]. Ca2+ preconditioning also protects human myocardium against I/R injury and protects rat hearts against post-ischemic myocardial dysfunction [106,107].

Expectedly, activation of AMPK also plays a central role in preconditioning-induced neuroprotection. Cortical spreading depression (CSD) is a phenomenon characterized by a wave of neuronal depolarization in the cortex followed by a period of quiescence that is associated with increases in metabolic rate and cerebral blood flow [108]. CSD may be induced experimentally by electrical stimulation or treatment with KCl, has been found to occur in the human cerebral cortex, and CSD-induced preconditioning of the brain enhances tolerance to subsequent ischemic insults [108,109]. Viggiano et al. showed that CSD induced by KCl (which activates AMPK in visual cortical neurons) led to a significant increase in AMPK activation which was predominately associated with neurons in the superficial layers of the cerebral cortex in rats [33,110]. KCl-induced CSD preconditioning also activated AMPK in the rat cortex and significantly alleviated neurological deficits in a middle cerebral artery occlusion I/R injury model that was mitigated by an autophagy inhibitor [111]. The AMPK inhibitor compound C however downregulated the protein levels of the autophagy markers ULK1 and LC3-II, indicating that the neuroprotective effects of CSD preconditioning are likely AMPK-dependent [111]. Additionally, ischemic preconditioning-induced neuroprotection was shown to be AMPK-dependent in a rat model of ischemic stroke and the AMPK activator AICAR protects primary mouse cortical neurons from NMDA-induced excitotoxicity, providing further evidence that AMPK activation plays a central role in stress-induced preconditioning of the brain [112,113].

Because nearly every neurotransmitter that promotes wakefulness, arousal, and consciousness activates AMPK and because nearly all general anesthetics used clinically activate AMPK, it would be expected that both neurotransmitters and anesthetics also act as preconditioning agents. Such a notion would also imply that cellular stress-induced AMPK activation is a common mechanism that potentially underlies and links preconditioning with paradoxical excitation, accelerated emergence from anesthesia, and restoration of consciousness (discussed in the next section). Indeed, glutamate preconditioning of rat cortical neurons exerts a neuroprotective effect against oxygen/glucose deprivation, acetylcholine-mediated preconditioning reduces infarct size in a rat model of I/R injury, and dopamine preconditioning significantly reduces infarct size in hyperlipidemic rat hearts [114–116]. Endogenous histamine mediates hypoxic preconditioning-induced stroke tolerance in mice, norepinephrine-induced preconditioning of rat hearts is cardioprotective in an I/R injury model, and serotonin protects mouse cortical neurons from methylmercury-induced cytotoxicity [117–119].

Preconditioning with the widely-used general anesthetic propofol exerts a protective effect against I/R injury in human hepatocytes, sevoflurane preconditioning enhances endogenous neurogenesis in the subventricular zone and is neuroprotective in a rat model of ischemic brain injury, and short-term isoflurane preconditioning protects rat primary cortical neurons against neurotoxicity induced by subsequent longer exposures to isoflurane [120–122]. Strikingly, slow intravenous injections of low-dose propofol to adult surgical patients resulted in low-pain intensity whereas venous occlusion-induced sustained exposure to propofol did not prolong pain, indicating that low-dose propofol may act as a preconditioning agent to reduce injection-site pain resulting from subsequent high-dose propofol injections [135]. Low-dose ketamine preconditioning also exerts a protective effect after induction of pneumoperitoneum (presence of gas or air in the abdominal cavity) in rats, dexmedetomidine preconditioning of rat brain cortical cultures demonstrated neuroprotective effects in an *in vitro* model of cerebral ischemia, and midazolam preconditioning enhances the protective effect of human bone marrow-derived mesenchymal stem cells in a rat model of hepatic I/R injury [123–125]. The GABAA receptor antagonists flumazenil and bicuculline, the anesthetic gas xenon, and the opioid analgesic remifentanil (commonly used during general anesthesia) each act as preconditioning agents, indicating that xenon, remifentanil, and flumazenil are also AMPK activators [48,126–128].

Recent evidence also suggests that various general anesthetics may share a common mechanism with the anti-diabetic drug metformin to induce AMPK activation. Similar to propofol and sevoflurane, metformin increases intracellular Ca2+ and ROS levels and acts as a neuroprotective preconditioning agent against focal cerebral ischemia in an AMPK-dependent manner [129–131]. A well-studied mechanism through which metformin induces AMPK activation is through mild inhibition of complex I of the mitochondrial electron transport chain (ETC), leading to the induction of cellular stress [19]. Mutations in a subunit of complex I of the mitochondrial ETC in *C. elegans* leads to immobilization (analogous to LOC and LORR) at lower concentrations of volatile anesthetics compared to wild-type animals, suggesting that in addition to the GABAA and NMDA receptors, the mitochondrial ETC is a potential target of anesthetic drugs [132]. AMPK activation may result from mitochondrial ETC inhibition, as *C. elegans* exhibits a paradoxical increase in movement when initially exposed to volatile anesthetics whereas a loss of neural AMPK/aak-2 inhibits movement [69–71]. A similar effect has also been observed in mice, where inactivation of a subunit of complex I of the mitochondrial ETC led to a 2.5–3.0 fold increase in sensitivity to volatile anesthetics (loss of response to tail clamp) and a 2-fold increase in sensitivity to propofol (LORR) compared to wild-type mice [133]. Propofol has also been shown to inhibit mitochondrial ETC function and increase ROS levels in human neuroblastoma SH-SY5Y cells, effects that were enhanced via the addition of metformin [136]. Inhibition of mitochondrial function contributes to the pathophysiology of propofol infusion syndrome (PRIS), a potentially fatal condition associated with prolonged exposure to propofol in high doses [137,138]. Additionally, Morgan et al. showed that pediatric patients exhibiting mitochondrial deficiencies including defects associated with complex I of the ETC displayed hypersensitivity to sevoflurane, providing further evidence that the mitochondrial ETC is a likely anesthetic target and that mild inhibition of the ETC by low-dose anesthetics may induce beneficial AMPK activation, possibly contributing to both preconditioning and paradoxical excitation [134].

Compounds & anesthetics that accelerate emergence from anesthesia and potentially enhance recovery from disorders of consciousness likely do so via AMPK

Unlike induction, emergence from GA is a passive process that occurs after removal of anesthesia and can be assessed by a patient's response to a verbal command [3,7,8]. Because nearly every neurotransmitter that promotes wakefulness, arousal, and consciousness activates AMPK (i.e. glutamate, acetylcholine, histamine, orexin-A, dopamine, and norepinephrine), it is likely that cellular stress-induced AMPK activation in neurons plays a pivotal role in accelerating emergence from anesthesia and restoring consciousness [32,39–43]. Evidence that stress mediates and enhances the activity of neurotransmitters is abundant in the plant kingdom. 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 (e.g. predator attack) and abiotic (e.g. drought) stressors have been well-described to increase the production and activity of these neurotransmitters in plants [139–141]. Toyota et al. recently demonstrated that wounding via scissors or caterpillar feeding on an

Arabidopsis plant led to an increase in both glutamate and Ca2+, with glutamate-induced activation of glutamate receptor-like ion channels generating intracellular Ca2+ concentrations that propagated to distal plant organs to induce a systemic defense response [141]. Several abiotic stressors (e.g. nutrient deficiency, osmotic and oxidative stress, etc.) also activate autophagy in *Arabidopsis* in an AMPK/SnRK1-dependent manner [142]. Fungal infection of certain rice cultivars increases the production of serotonin, which suppresses leaf damage and reduces biotic stress and the production of dopamine by the green alga *Ulvaria obscura* acts as a feeding deterrent against sea urchins, snails, and isopods [143,144]. Interestingly, just as various volatile anesthetics promote seed germination, certain plants have been shown to produce the anesthetic divinyl ether when stressed [74,145,146]. ROS and Ca2+ also play critical roles in the production of secondary metabolites, compounds that plants produce in response to stress partly for the purpose of self defense [147,148]. Moreover, the GABAA receptor antagonist bicuculline, a secondary metabolite produced by the plant *Corydalis chaerophylla*, reverses propofol anesthesia and activates AMPK in cortical neurons, suggesting that a mechanism of cellular stress-induced AMPK activation by neurotransmitters may have been evolutionarily conserved to promote neuronal activation in the human brain [45,46,149,150].

Several plant-derived secondary metabolites have also been shown to accelerate emergence from anesthesia in animal models and in humans. The secondary metabolites forskolin (derived from the plant *Plectranthus barbatus*) and caffeine (derived from numerous plants) both activate AMPK and dramatically accelerate emergence from isoflurane anesthesia in rats while caffeine also accelerates emergence from anesthesia in propofol-anesthetized rats [20,21,151–153]. Similar to the anesthetic ketamine and increases in intracellular ROS and Ca2+, forskolin also promotes LTP in hippocampal slices [25,28–30,96,154]. A recent randomized, double-blind, crossover study further demonstrated that an intravenous infusion of caffeine led to a 42% reduction in the mean time to emergence in healthy males anesthetized with isoflurane compared to placebo, indicating that compounds that activate AMPK are capable of accelerating emergence from anesthesia in humans [155]. Additionally, intrathalamic microinfusion of nicotine, a well-studied secondary metabolite derived from the plant *Nicotiana attenuata*, reverses sevoflurane-induced unconsciousness (i.e. LORR) in rats [156,157]. Nicotine also enhances hippocampal CA1 LTP in mice and both nicotine and metformin activate AMPK in the hippocampus *in vivo* in mice [22,158]. Interestingly, metformin was originally derived from a secondary metabolite found in the plant *Galega officinalis* [19,159]. Physostigmine, a secondary metabolite found in the plant *Physostigma venenosum*, increases acetylcholine levels through reversible inhibition of acetylcholinesterase and restores consciousness in human volunteers anesthetized with propofol [160,161]. Additionally, acetylcholine activates AMPK and stimulation of the prefrontal cortex with the cholinergic agonist carbachol reversed sevoflurane anesthesia and restored wake-like behavior in rats [39,162]. As carbachol activates AMPK in human neuroblastoma SH-SY5Y cells, cellular stress-induced AMPK activation likely also plays a role in physostigmine-induced restoration of consciousness in humans [163]. Furthermore, a ketogenic diet (i.e. high fat/low carbohydrate diet) or a standard diet supplemented with the exogenous ketone body beta-hydroxybutyrate (βHB) significantly delayed the onset of isoflurane-induced anesthesia in rats [164]. βHB activates AMPK and a ketogenic diet transiently increases the levels of ROS in the hippocampus *in vivo* in rats, providing compelling evidence that cellular stress-induced AMPK activation promotes delayed induction of and accelerated emergence from anesthesia [165,166].

As glutamate and nearly every neurotransmitter released from ascending arousal circuits that promote wakefulness, arousal, and consciousness activates AMPK, it would be expected that compounds or methodologies that enhance neurotransmitter activity would also accelerate emergence from anesthesia [32,39–43]. Dextroamphetamine, which induces the release of dopamine, significantly accelerates emergence from both sevoflurane and propofol anesthesia whereas the D1 dopamine receptor antagonist SCH-23390 inhibited chloro-APB (a D1 receptor agonist)-mediated restoration of righting and emergence from isoflurane anesthesia in rats [167,168]. The selective D1 receptor agonist fenoldopam however activates AMPK in human monocytes [43]. Microinjection of orexin-A into the basal forebrain of rats also facilitated emergence from propofol anesthesia [169]. Rao et al. demonstrated that prolonged wakefulness in mice, which activates AMPK, produces LTP of glutamatergic synapses on orexin neurons. The D1 dopamine receptor antagonist SCH-23390 however attenuated synaptic plasticity whereas forskolin induced LTP in orexin neurons, providing further evidence that cellular stress-induced AMPK activation links LTP and restoration of consciousness [21,24–30,56,170].

Activation of glutamatergic neurons in the parabrachial nucleus (located in the brain stem) accelerated emergence from sevoflurane anesthesia in mice and also prolonged induction time, similar to ketone body/ketogenic diet-induced delayed onset of isoflurane anesthesia in rats [164,171]. Strikingly, propofol was recently shown to induce an abrupt increase in Ca2+ levels in parabrachial nucleus neurons *in vivo* just before LORR and recovery of righting reflex (RORR) in rats, indicating that propofol is excitatory at low doses and promotes paradoxical excitation and possible facilitation of return of consciousness via cellular stress induction (i.e. Ca2+ and/or ROS) and AMPK activation [192]. Microinjections of histamine into the nucleus basalis magnocellularis located in the basal forebrain also facilitates emergence from isoflurane anesthesia and induces EEG arousal in rats [172]. Delivery of noradrenaline (also known as norepinephrine) into the prefrontal cortex led to EEG activation but did not induce behavioral signs of arousal in rats anesthetized with sevoflurane [162]. However, infusion of orexin-A into the locus ceruleus promotes norepinephrine-induced LTP in the dentate gyrus of the rat hippocampus and stimulation of serotonergic axons in the hippocampal CA1 region enhances spatial memory in mice, similar to nicotine, forskolin, and ketamine [96,154,158,173,174]. Moreover, as the anesthetic ketamine induces antidepressant effects in rats by activating AMPK and nearly every general anesthetic used clinically induces AMPK activation similar to neurotransmitters, it would also be expected that certain anesthetic drugs may paradoxically accelerate emergence from anesthesia [93]. Hambrecht-Wiedbusch et al. showed that injection of a single dose of subanesthetic ketamine initially increased anesthetic depth in isoflurane-anesthetized rats but also increased cortical acetylcholine release and paradoxically accelerated emergence and recovery of consciousness, again suggesting that AMPK activation represents a common mechanism linking neurotransmitter- and low-dose anesthetic-induced restoration of consciousness [175].

Lastly, cellular stress-induced AMPK activation may also prove effective for individuals affected by disorders of consciousness. Disorders of consciousness include a minimally conscious state, vegetative state, and coma and often stem from traumatic or non-traumatic injuries to the brain [176]. Patients in a minimally conscious state exhibit significantly impaired consciousness with intermittent periods of self-awareness whereas a vegetative state is characterized by wakefulness without cognition and self-awareness [3,176]. Coma is a deep state of unconsciousness characterized by abnormal brain stem reflexes and a lack of wakefulness and awareness [176]. Neurogenesis, a process of generating neurons from neural stem or progenitor cells (NSCs), has been shown to occur in the adult mammalian brain in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and in the subventricular zone (SVZ) of the lateral ventricles [177]. Cellular stress (e.g. ROS) induces differentiation of embryonic and adult stem cells, ischemia stimulates neurogenesis in the SGZ and SVZ in rats *in vivo*, and the SVZ lies in close proximity to the cerebral cortex [52,177,178]. Because metformin promotes neurogenesis in both the SGZ and the SVZ *in vitro* and *in vivo*, compounds that activate AMPK via the induction of cellular stress may enhance brain repair and potentially facilitate

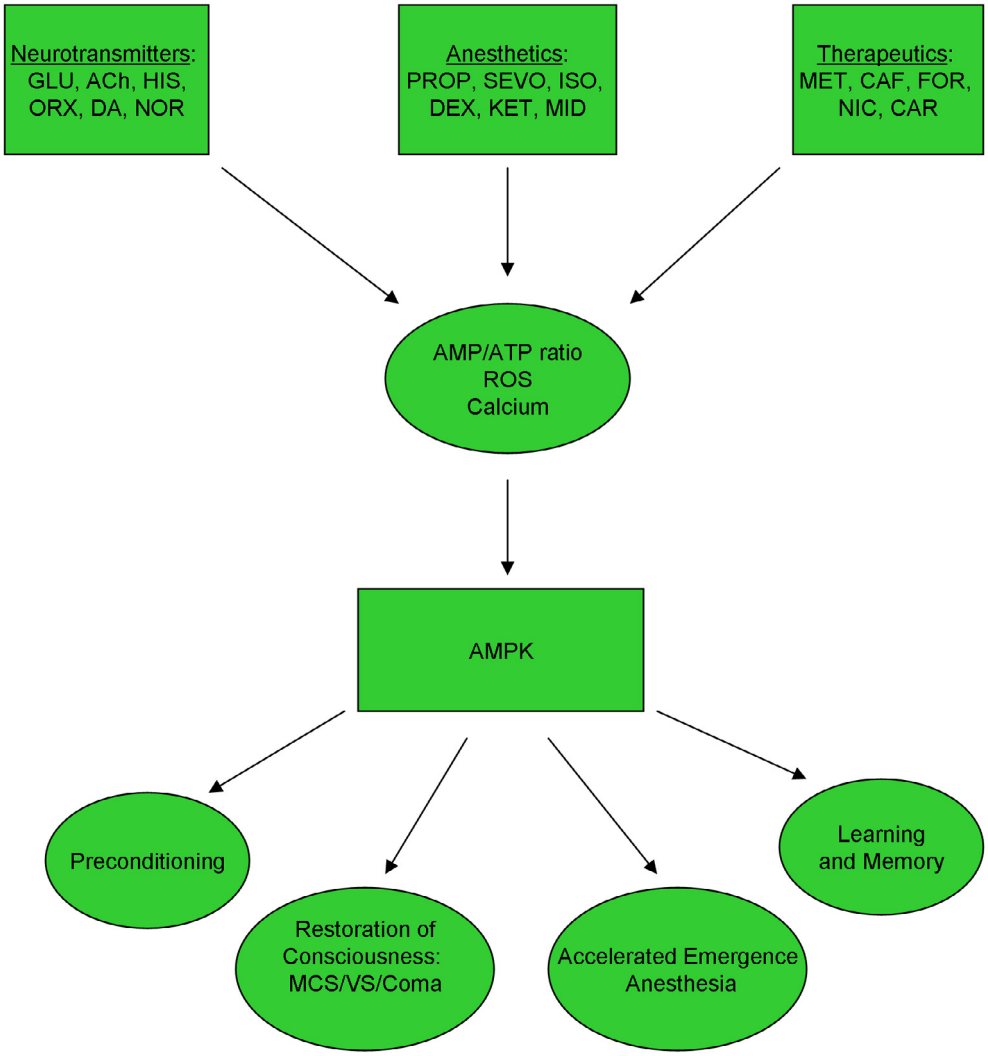

Fig. 1. Proposed mechanisms that link cellular stress and AMPK activation with accelerated emergence from anesthesia, restoration of consciousness in disorders of consciousness, learning and memory, and preconditioning. AMPK: AMP-activated protein kinase, AMP: adenosine monophosphate, ATP: adenosine triphosphate, ROS: reactive oxygen species, PROP: propofol, SEVO: sevoflurane, ISO: isoflurane, DEX: dexmedetomidine, KET: ketamine, MID: midazolam, GLU: Glutamate, Ach: acetylcholine, HIS: histamine, ORX: orexin-A, DA: dopamine, NOR: norepinephrine, MET: metformin, CAF: caffeine, FOR: forskolin, NIC: nicotine, CAR: carbachol.

restoration of consciousness in patients with disorders of consciousness [179–182]. Moreover, evidence also indicates that cellular stress and AMPK activation may link human consciousness with seemingly disparate physiological and pathophysiological phenomena, including accelerated aging, HIV-1, human reproduction, cancer, gene regulation (e.g. transposable elements), plasma medicine, cell cycle regulation, meditation, fetal hemoglobin induction, parabiosis (i.e. young blood), planarian regeneration, and stress-induced CRISPR-Cas activation in bacteria (e.g. gene editing technology) [24,52,183–187,193–202].

Hypothesis testing

AMPK knockdown or pharmacological inhibition in various brain structures (e.g. basal forebrain, cerebral cortex, thalamus, hypothalamus, brain stem, etc.) would be necessary to determine if AMPK activation is essential in facilitating accelerated emergence from anesthesia induced by certain compounds (e.g. caffeine, forskolin, methylphenidate, etc.). Appropriately designed and approved case studies using AMPK activators that possess exemplary safety profiles (e.g. metformin, caffeine, etc.) would also indicate if AMPK activation plays a beneficial role in restoration of consciousness in patients diagnosed with disorders of consciousness (i.e. minimally conscious state, vegetative state, coma).

Conclusion

In conclusion, cellular stress-induced AMPK activation, mediated by increases in intracellular ROS, $Ca2+$, and/or an AMP(ADP)/ATP ratio increase, etc. links wakefulness, arousal, and consciousness with paradoxical excitation and accelerated emergence from anesthesia (Fig. 1). AMPK is located throughout the brain and is activated by nearly every neurotransmitter that promotes arousal and consciousness, including glutamate, acetylcholine, histamine, orexin-A, dopamine, and norepinephrine. Nearly every anesthetic used clinically to promote LOC in human patients induces paradoxical excitation in low doses and also activates AMPK (i.e. propofol, sevoflurane, isoflurane, dexmedetomidine, ketamine, and midazolam). Because anesthetic brain concentrations are significantly higher during induction than at emergence, cellular stress-induced AMPK activation by low doses of anesthetics and neurotransmitters link paradoxical excitation with accelerated emergence from anesthesia and return of consciousness. Additionally, several general anesthetics and neurotransmitters act as preconditioning agents and increases in ROS, $Ca2+$, and AMPK activation have been shown to exert preconditioning effects, indicating that paradoxical

excitation is analogous to preconditioning and both likely share a common mechanism of AMPK activation. Also, metformin, an AMPK activator with an exceptional safety profile that crosses the blood-brain barrier *in vivo*, induces proliferation and differentiation of neural stem cells in the dentate gyrus and subventricular zone, indicating that AMPK activation may promote brain repair and restoration of consciousness in patients diagnosed with disorders of consciousness (i.e. minimally conscious state, vegetative state, coma).

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.01.014.

References

[1] Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci 2011;34:601–28.
[2] Uhrig L, Dehaene S, Jarraya B. Cerebral mechanisms of general anesthesia. Ann Fr Anesth Reanim 2014;33(2):72–82.
[3] Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010;363(27):2638–50.
[4] Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci 2008;9(5):370–86.
[5] McCarthy MM, Brown EN, Kopell N. Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. J Neurosci 2008;28(50):13488–504.
[6] Grønli J, Rempe MJ, Clegern WC, Schmidt M, Wisor JP. Beta EEG reflects sensory processing in active wakefulness and homeostatic sleep drive in quiet wakefulness. J Sleep Res 2016;25(3):257–68.
[7] Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: part I: background and basic signatures. Anesthesiology 2015;123(4):937–60.
[8] Tarnal V, Vlisides PE, Mashour GA. The neurobiology of anesthetic emergence. J Neurosurg Anesthesiol 2016;28(3):250–5.
[9] Garcia PS, Kolesky SE, Jenkins A. General anesthetic actions on GABA(A) receptors. Curr Neuropharmacol 2010;8(1):2–9.
[10] Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14(1):13–21.
[11] Muindi F, Kenny JD, Taylor NE, et al. Electrical stimulation of the parabrachial nucleus induces reanimation from isoflurane general anesthesia. Behav Brain Res 2016;1(306):20–5.
[12] Lage R, Diéguez C, Vidal-Puig A, López M. AMPK: a metabolic gauge regulating whole-body energy homeostasis. Trends Mol Med 2008;14(12):539–49.
[13] Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. Ageing Res Rev 2012;11(2):230–41.
[14] Sook SH, Lee HJ, Kim JH, et al. Reactive oxygen species-mediated activation of AMP-activated protein kinase and c-Jun N-terminal kinase plays a critical role in beta-sitosterol-induced apoptosis in multiple myeloma U266 cells. Phytother Res 2014;28(3):387–94.
[15] Uittenbogaard M, Chiaramello. Mitochondrial biogenesis: a therapeutic target for neurodevelopmental disorders and neurodegenerative diseases. Curr Pharm Des 2014;20(35):5574–93.
[16] Du LL, Chai DM, Zhao LN, et al. AMPK activation ameliorates Alzheimer's disease-like pathology and spatial memory impairment in a streptozotocin-induced Alzheimer's disease model in rats. J Alzheimers Dis 2015;43(3):775–84.
[17] Lu M, Su C, Qiao C, Bian Y, Ding J, Hu G. Metformin prevents dopaminergic neuron death in MPTP/P-induced mouse model of parkinson's disease via autophagy and mitochondrial ROS clearance. Int J Neuropsychopharmacol 2016;19(9). pii: pyw047.
[18] Jin J, Gu H, Anders NM, et al. Metformin protects cells from mutant Huntingtin toxicity through activation of AMPK and modulation of mitochondrial dynamics. Neuromol Med 2016;18(4):581–92.
[19] Hardie DG. AMPK: a target for drugs and natural products with effects on both diabetes and cancer. Diabetes 2013;62(7):2164–72.
[20] Jensen TE, Rose AJ, Hellsten Y, Wojtaszewski JF, Richter EA. Caffeine-induced Ca (2+) release increases AMPK-dependent glucose uptake in rodent soleus muscle. Am J Physiol Endocrinol Metab 2007;293(1):E286–92.
[21] Egawa M, Kamata H, Kushiyama A, et al. Long-term forskolin stimulation induces AMPK activation and thereby enhances tight junction formation in human placental trophoblast BeWo cells. Placenta 2008;29(12):1003–8.
[22] Brynildsen JK, Lee BG, Perron IJ, Jin S, Kim SF, Blendy JA. Activation of AMPK by metformin improves withdrawal signs precipitated by nicotine withdrawal. Proc Natl Acad Sci U S A 2018;115(16):4282–7.
[23] Culmsee C, Monnig J, Kemp BE, Mattson MP. AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation. J Mol Neurosci 2001;17(1):45–58.
[24] Finley J. Facilitation of hippocampal long-term potentiation and reactivation of latent HIV-1 via AMPK activation: common mechanism of action linking learning, memory, and the potential eradication of HIV-1. Med Hypotheses 2018;116:61–73.
[25] Volianskis A, France G, Jensen MS, et al. Long-term potentiation and the role of N-methyl-D-aspartate receptors. Brain Res 2015;24(1621):5–16.
[26] Görlach A, Bertram K, Hudecova S, Krizanova O. Calcium and ROS: a mutual interplay. Redox Biol 2015;6:260–71.
[27] Bindokas VP, Jordán J, Lee CC, Miller RJ. Superoxide production in rat hippocampal neurons: selective imaging with hydroethidine. J Neurosci 1996;16(4):1324–36.
[28] Knapp LT, Klann E. Potentiation of hippocampal synaptic transmission by superoxide requires the oxidative activation of protein kinase C. J Neurosci 2002;22(3):674–83.
[29] Klann E. Cell-permeable scavengers of superoxide prevent long-term potentiation in hippocampal area CA1. J Neurophysiol 1998;80(1):452–7.
[30] Thiels E, Urban NN, Gonzalez-Burgos GR, et al. Impairment of long-term potentiation and associative memory in mice that overexpress extracellular superoxide dismutase. J Neurosci 2000;20(20):7631–9.
[31] Potter WB, O'Riordan KJ, Barnett D, et al. Metabolic regulation of neuronal plasticity by the energy sensor AMPK. PLoS One 2010;5(2):e8996.
[32] Terunuma M, Vargas KJ, Wilkins ME, et al. Prolonged activation of NMDA receptors promotes dephosphorylation and alters postendocytic sorting of GABAB receptors. Proc Natl Acad Sci U S A 2010;107(31):13918–23.
[33] Chen X, Zhao X, Zhang M, Wei S. Nuclear respiratory factor-2α and adenosine triphosphate synapses in rat primary cortical neuron cultures: the key role of adenosine monophosphate-activated protein kinase. Mol Med Rep 2015;12(4):6323–9.
[34] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays Biochem 2010;47:69–84.
[35] El-Mir MY, Detaille D, R-Villanueva G, et al. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Mol Neurosci 2008;34(1):77–87.
[36] Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology 2003;28(2):216–25.
[37] Kharazia VN, Weinberg RJ. Glutamate in thalamic fibers terminating in layer IV of primary sensory cortex. J Neurosci 1994;14(10):6021–32.
[38] Kuo MC, Dringenberg H. Histamine facilitates in vivo thalamocortical long-term potentiation in the mature visual cortex of anesthetized rats. Eur J Neurosci 2008;27(7):1731–8.
[39] Zhao M, Sun L, Yu XJ, et al. Acetylcholine mediates AMPK-dependent autophagic cytoprotection in H9c2 cells during hypoxia/reoxygenation injury. Cell Physiol Biochem 2013;32(3):601–13.
[40] Wu WN, Wu PF, Zhou J, et al. Orexin-A activates hypothalamic AMP-activated protein kinase signaling through a Ca^{2+}-dependent mechanism involving voltage-gated L-type calcium channel. Mol Pharmacol 2013;84(6):876–87.
[41] Thors B, Halldórsson H, Thorgeirsson G. eNOS activation mediated by AMPK after stimulation of endothelial cells with histamine or thrombin is dependent on LKB1. Biochim Biophys Acta 2011;1813(2):322–31.
[42] Hutchinson DS, Chernogubova E, Dallner OS, Cannon B, Bengtsson T. Beta-adrenoceptors, but not alpha-adrenoceptors, stimulate AMP-activated protein kinase in brown adipocytes independently of uncoupling protein-1. Diabetologia 2005;48(11):2386–95.
[43] Bone NB, Liu Z, Pittet JF, Zmijewski JW. Frontline Science: D1 dopaminergic receptor signaling activates the AMPK-bioenergetic pathway in macrophages and alveolar epithelial cells and reduces endotoxin-induced ALI. J Leukoc Biol 2017;101(2):357–65.
[44] Laporta J, Peters TL, Merriman KE, Vezina CM, Hernandez LL. Serotonin (5-HT) affects expression of liver metabolic enzymes and mammary gland glucose transporters during the transition from pregnancy to lactation. PLoS One 2013;8(2):e57847.
[45] Irifune M, Sugimura M, Takarada T, et al. Propofol anaesthesia in mice is potentiated by muscimol and reversed by bicuculline. Br J Anaesth 1999;83(4):665–7.
[46] Kenney JW, Sorokina O, Genheden M, Sorokin A, Armstrong JD, Proud CG. Dynamics of elongation factor 2 kinase regulation in cortical neurons in response to synaptic activity. J Neurosci. 2015;35(7):3034–47.
[47] Kim YJ, Lee H, Kim CH, Lee GY, Baik HJ, Han JI. Effect of flumazenil on recovery from anesthesia and the bispectral index after sevoflurane/fentanyl general anesthesia in unpremedicated patients. Korean J Anesthesiol 2012;62(1):19–23.
[48] Yao Z, McPherson BC, Liu H, et al. Signal transduction of flumazenil-induced preconditioning in myocytes. Am J Physiol Heart Circ Physiol 2001;280(3):H1249–55.
[49] Yoshiike Y, Kimura T, Yamashita S, et al. GABA(A) receptor-mediated acceleration of aging-associated memory decline in APP/PS1 mice and its pharmacological treatment by picrotoxin. PLoS One 2008;3(8):e3029.
[50] Colas D, Chuluun B, Garner CC, Heller HC. Short-term treatment with flumazenil restores long-term object memory in a mouse model of Down syndrome. Neurobiol Learn Mem 2017;140:11–6.
[51] Fernandez F, Morishita W, Zuniga E, et al. Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. Nat Neurosci 2007;10(4):411–3.
[52] Finley J. Elimination of cancer stem cells and reactivation of latent HIV-1 via AMPK activation: common mechanism of action linking inhibition of

tumorigenesis and the potential eradication of HIV-1. Med Hypotheses 2017;104:133–46.
[53] Valenti D, de Bari L, de Rasmo D, et al. The polyphenols resveratrol and epigallocatechin-3-gallate restore the severe impairment of mitochondria in hippocampal progenitor cells from a Down syndrome mouse model. Biochim Biophys Acta 2016;1862(6):1093–104.
[54] Izzo A, Nitti M, Mollo N, et al. Metformin restores the mitochondrial network and reverses mitochondrial dysfunction in Down syndrome cells. Hum Mol Genet 2017;26(6):1056–69.
[55] Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. Acta Anaesthesiol Scand 2008;52(2):289–94.
[56] Dworak M, McCarley RW, Kim T, Kalinchuk AV, Basheer R. Sleep and brain energy levels: ATP changes during sleep. J Neurosci 2010;30(26):9007–16.
[57] Nikonova EV, Naidoo N, Zhang L, et al. Changes in components of energy regulation in mouse cortex with increases in wakefulness. Sleep 2010;33(7):889–900.
[58] Grassi Zucconi G, Cipriani S, Balgkouranidou I, Scattoni R. 'One night' sleep deprivation stimulates hippocampal neurogenesis. Brain Res Bull 2006;69(4):375–81.
[59] Boland EM, Rao H, Dinges DF, et al. Meta-analysis of the antidepressant effects of acute sleep deprivation. J Clin Psychiatry 2017;78(8):e1020–34.
[60] Dworak M, Kim T, Mccarley RW, Basheer R. Creatine supplementation reduces sleep need and homeostatic sleep pressure in rats. J Sleep Res 2017;26(3):377–85.
[61] Ceddia RB, Sweeney G. Creatine supplementation increases glucose oxidation and AMPK phosphorylation and reduces lactate production in L6 rat skeletal muscle cells. J Physiol 2004;555(Pt 2):409–21.
[62] Dworak M, McCarley RW, Kim T, Basheer R. Delta oscillations induced by ketamine increase energy levels in sleep-wake related brain regions. Neuroscience 2011;1(197):72–9.
[63] Butelman ER, Woods JH. Effects of clonidine, dexmedetomidine and xylazine on thermal antinociception in rhesus monkeys. J Pharmacol Exp Ther 1993;264(2):762–9.
[64] Kim SS, Park SH, Lee JR, Jung JS, Suh HW. The activation of α2-adrenergic receptor in the spinal cord lowers sepsis-induced mortality. Korean J Physiol Pharmacol 2017;21(5):495–507.
[65] Xu SX, Zhou ZQ, Li XM, Ji MH, Zhang GF, Yang JJ. The activation of adenosine monophosphate-activated protein kinase in rat hippocampus contributes to the rapid antidepressant effect of ketamine. Behav Brain Res 2013;15(253):305–9.
[66] Shi XX, Yin BS, Yang P, et al. Xylazine activates adenosine monophosphate-activated protein kinase pathway in the central nervous system of rats. PLoS One 2016;11(4):e0153169.
[67] Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth 2001;87(3):421–8.
[68] Friedman EB, Sun Y, Moore JT, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. PLoS One 2010;5(7):e11903.
[69] Morgan PG, Kayser EB, Sedensky MM. *C. elegans* and volatile anesthetics. WormBook 2007;3:1–11.
[70] Morgan PG, Cascorbi HF. Effect of anesthetics and a convulsant on normal and mutant *Caenorhabditis elegans*. Anesthesiology 1985;62(6):738–44.
[71] Cunningham KA, Bouagnon AD, Barros AG, et al. Loss of a neural AMP-activated kinase mimics the effects of elevated serotonin on fat, movement, and hormonal secretions. PLoS Genet 2014;10(6):e1004394.
[72] Jia B, Crowder CM. Volatile anesthetic preconditioning present in the invertebrate *Caenorhabditis elegans*. Anesthesiology 2008;108(3):426–33.
[73] Yokawa K, Kagenishi T, Pavlovic A, et al. Anaesthetics stop diverse plant organ movements, affect endocytic vesicle recycling and ROS homeostasis, and block action potentials in Venus flytraps. Ann Bot 2017. https://doi.org/10.1093/aob/mcx155. [Epub ahead of print].
[74] Taylorson RB, Hendricks SB. Overcoming dormancy in seeds with ethanol and other anesthetics. Planta 1979;145(5):507–10.
[75] Leymarie J, Vitkauskaité G, Hoang HH, et al. Role of reactive oxygen species in the regulation of Arabidopsis seed dormancy. Plant Cell Physiol 2012;53(1):96–106.
[76] Gao XQ, Liu CZ, Li DD, et al. The arabidopsis KINβγ Subunit of the SnRK1 complex regulates pollen hydration on the stigma by mediating the level of reactive oxygen species in pollen. PLoS Genet 2016;12(7):e1006228.
[77] Duan Q, Kita D, Johnson EA, et al. Reactive oxygen species mediate pollen tube rupture to release sperm for fertilization in Arabidopsis. Nat Commun 2014;5:3129.
[78] Chen X, Li LY, Jiang JL, et al. Propofol elicits autophagy via endoplasmic reticulum stress and calcium exchange in C2C12 myoblast cell line. PLoS One 2018;13(5):e0197934.
[79] Chen X, Li K, Zhao G. Propofol inhibits HeLa cells by impairing autophagic flux via AMP-activated protein kinase (AMPK) activation and endoplasmic reticulum stress regulated by calcium. Med Sci Monit 2018;18(24):2339–49.
[80] Sall JW, Stratmann G, Leong J, Woodward E, Bickler PE. Propofol at clinically relevant concentrations increases neuronal differentiation but is not toxic to hippocampal neural precursor cells in vitro. Anesthesiology 2012;117(5):1080–90.
[81] Tao T, Zhao Z, Hao L, Gu M, Chen L, Tang J. Propofol promotes proliferation of cultured adult rat hippocampal neural stem cells. J Neurosurg Anesthesiol 2013;25(3):299–305.
[82] Qiao H, Li Y, Xu Z, et al. Propofol affects neurodegeneration and neurogenesis by regulation of autophagy via effects on intracellular calcium homeostasis. Anesthesiology 2017;127(3):490–501.
[83] Wu GJ, Chen WF, Hung HC, et al. Effects of propofol on proliferation and anti-apoptosis of neuroblastoma SH-SY5Y cell line: new insights into neuroprotection. Brain Res 2011;12(1384):42–50.
[84] Fischer MJ, Leffler A, Niedermirtl F, et al. The general anesthetic propofol excites nociceptors by activating TRPV1 and TRPA1 rather than GABAA receptors. J Biol Chem 2010;285(45):34781–92.
[85] Kim YJ, Lee DH, Ahn J, et al. Pharmacokinetics, tissue distribution, and anti-lipogenic/adipogenic effects of allyl-isothiocyanate metabolites. PLoS One 2015;10(8):e0132151.
[86] Kim SH, Hwang JT, Park HS, Kwon DY, Kim MS. Capsaicin stimulates glucose uptake in C2C12 muscle cells via the reactive oxygen species (ROS)/AMPK/p38 MAPK pathway. Biochem Biophys Res Commun 2013;439(1):66–70.
[87] Lamberts RR, Onderwater G, Hamdani N, et al. Reactive oxygen species-induced stimulation of 5'AMP-activated protein kinase mediates sevoflurane-induced cardioprotection. Circulation 2009;120(11 Suppl):S10–5.
[88] Song T, Lv LY, Xu J, et al. Diet-induced obesity suppresses sevoflurane preconditioning against myocardial ischemia-reperfusion injury: role of AMP-activated protein kinase pathway. Exp Biol Med (Maywood) 2011;236(12):1427–36.
[89] Pinheiro AC, Gomez RS, Guatimosim C, Silva JH, Prado MA, Gomez MV. The effect of sevoflurane on intracellular calcium concentration from cholinergic cells. Brain Res Bull 2006;69(2):147–52.
[90] Alkire MT, Nathan SV, McReynolds JR. Memory enhancing effect of low-dose sevoflurane does not occur in basolateral amygdala-lesioned rats. Anesthesiology 2005;103(6):1167–73.
[91] Rao Z, Pan X, Zhang H, et al. Isoflurane preconditioning alleviated murine liver ischemia and reperfusion injury by restoring AMPK/mTOR-mediated autophagy. Anesth Analg 2017;125(4):1355–63.
[92] Zhao X, Yang Z, Liang G, et al. Dual effects of isoflurane on proliferation, differentiation, and survival in human neuroprogenitor cells. Anesthesiology 2013;118(3):537–49.
[93] Xu SX, Zhou ZQ, Li XM, et al. The activation of adenosine monophosphate-activated protein kinase in rat hippocampus contributes to the rapid antidepressant effect of ketamine. Behav Brain Res 2013;15(253):305–9.
[94] Lepack AE, Fuchikami M, Dwyer JM, Banasr M, Duman RS. BDNF release is required for the behavioral actions of ketamine. Int J Neuropsychopharmacol 2014;18(1). pii: pyu033.
[95] Zuo DY, Wu YL, Yao WX, Cao Y, Wu CF, Tanaka M. Effect of MK-801 and ketamine on hydroxyl radical generation in the posterior cingulate and retrosplenial cortex of free-moving mice, as determined by in vivo microdialysis. Pharmacol Biochem Behav 2007;86(1):1–7.
[96] Widman AJ, Stewart AE, Erb EM, Gardner E, McMahon LL. Intravascular ketamine increases theta-burst but not high frequency tetanus induced LTP at CA3-CA1 synapses within three hours and devoid of an increase in spine density. Front Synaptic Neurosci 2018;30(10):8.
[97] Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry 2018;175(7):620–30.
[98] Wang Z, Zhou W, Dong H, Ma X, He Z. Dexmedetomidine pretreatment inhibits cerebral ischemia/reperfusion induced neuroinflammation via activation of AMPK. Mol Med Rep 2018;18(4):3957–64.
[99] Shindo S, Numazawa S, Yoshida T. A physiological role of AMP-activated protein kinase in phenobarbital-mediated constitutive androstane receptor activation and CYP2B induction. Biochem J 2007;401(3):735–41.
[100] Schwer CI, Lehane C, Guelzow T, et al. Thiopental inhibits global protein synthesis by repression of eukaryotic elongation factor 2 and protects from hypoxic neuronal cell death. PLoS One 2013;8(10):e77258.
[101] Zhang Y, Tao GJ, Hu L, et al. Lidocaine alleviates morphine tolerance via AMPK-SOCS3-dependent neuroinflammation suppression in the spinal cord. J Neuroinflammation 2017;14(1):211.
[102] Calabrese EJ. Preconditioning is hormesis part I: documentation, dose-response features and mechanistic foundations. Pharmacol Res 2016;110:242–64.
[103] Calabrese EJ. Preconditioning is hormesis part II: how the conditioning dose mediates protection: dose optimization within temporal and mechanistic frameworks. Pharmacol Res 2016;110:265–75.
[104] Bhagatte Y, Lodwick D, Storey N. Mitochondrial ROS production and subsequent ERK phosphorylation are necessary for temperature preconditioning of isolated ventricular myocytes. Cell Death Dis 2012;5(3):e345.
[105] De Barros S, Dehez S, Arnaud E, et al. Aging-related decrease of human ASC angiogenic potential is reversed by hypoxia preconditioning through ROS production. Mol Ther 2013;21(2):399–408.
[106] Cain BS, Meldrum DR, Meng X, Shames BD, Banerjee A, Harken AH. Calcium preconditioning in human myocardium. Ann Thorac Surg 1998;65(4):1065–70.
[107] Meldrum DR, Cain BS, Meng X, et al. Calcium preconditioning, but not ischemic preconditioning, bypasses the adenosine triphosphate-dependent potassium (KATP) channel. J Surg Res 1999;85(1):77–82.
[108] Shen PP, Hou S, Ma D, et al. Cortical spreading depression-induced preconditioning in the brain. Neural Regen Res 2016;11(11):1857–64.
[109] Fabricius M, Fuhr S, Bhatia R, et al. Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain 2006;129(Pt 3):778–90.
[110] Viggiano E, Viggiano D, Viggiano A, De Luca B, Monda M. Cortical spreading depression increases the phosphorylation of AMP-activated protein kinase in the cerebral cortex. Neurochem Res 2014;39(12):2431–9.
[111] Shen P, Hou S, Zhu M, Zhao M, Ouyang Y, Feng J. Cortical spreading depression preconditioning mediates neuroprotection against ischemic stroke by inducing

AMP-activated protein kinase-dependent autophagy in a rat cerebral ischemic/reperfusion injury model. J Neurochem 2017;140(5):799–813.
[112] Jiang T, Yu JT, Zhu XC, et al. Ischemic preconditioning provides neuroprotection by induction of AMP-activated protein kinase-dependent autophagy in a rat model of ischemic stroke. Mol Neurobiol 2015;51(1):220–9.
[113] Anilkumar U, Weisová P, Düssmann H, Concannon CG, König HG, Prehn JH. AMP-activated protein kinase (AMPK)-induced preconditioning in primary cortical neurons involves activation of MCL-1. J Neurochem 2013;124(5):721–34.
[114] Lin CH, Chen PS, Gean PW. Glutamate preconditioning prevents neuronal death induced by combined oxygen-glucose deprivation in cultured cortical neurons. Eur J Pharmacol 2008;589(1–3):85–93.
[115] Qian YZ, Levasseur JE, Yoshida K, Kukreja RC. KATP channels in rat heart: blockade of ischemic and acetylcholine-mediated preconditioning by glibenclamide. Am J Physiol 1996;271(1 Pt 2):H23–8.
[116] Gupta V, Goyal R, Sharma PL. Preconditioning offers cardioprotection in hyperlipidemic rat hearts: possible role of Dopamine (D2) signaling. BMC Cardiovasc Disord 2015;28(15):77.
[117] Fan YY, Hu WW, Dai HB, et al. Activation of the central histaminergic system is involved in hypoxia-induced stroke tolerance in adult mice. J Cereb Blood Flow Metab 2011;31(1):305–14.
[118] Parikh V, Singh M. Possible role of cardiac mast cells in norepinephrine-induced myocardial preconditioning. Methods Find Exp Clin Pharmacol 1999;21(4):269–74.
[119] Olguín N, Müller ML, Rodríguez-Farré E, Suñol C. Neurotransmitter amines and antioxidant agents in neuronal protection against methylmercury-induced cytotoxicity in primary cultures of mice cortical neurons. Neurotoxicology 2018. https://doi.org/10.1016/j.neuro.2018.07.020. pii: S0161-813X(18)30309-7. [Epub ahead of print].
[120] Zhang Y, Chen Z, Feng N, et al. Protective effect of propofol preconditioning on ischemia-reperfusion injury in human hepatocyte. J Thorac Dis 2017;9(3):702–10.
[121] Li L, Saiyin H, Xie J, et al. Sevoflurane preconditioning induced endogenous neurogenesis against ischemic brain injury by promoting microglial activation. Oncotarget 2017;8(17):28544–57.
[122] Wei H, Liang G, Yang H. Isoflurane preconditioning inhibited isoflurane-induced neurotoxicity. Neurosci Lett 2007;425(1):59–62.
[123] Xingwei X, Xin G, Peng Z, et al. Low-dose ketamine pretreatment reduces oxidative damage and inflammatory response following CO2 pneumoperitoneum in rats. Clin Invest Med 2014;37(3):E124.
[124] Rodríguez-González R, Sobrino T, Veiga S, et al. Neuroprotective effects of dexmedetomidine conditioning strategies: evidences from an in vitro model of cerebral ischemia. Life Sci 2016;1(144):162–9.
[125] Feng J, Yao W, Zhang Y, Xiang AP, Yuan D, Hei Z. Intravenous anesthetics enhance the ability of human bone marrow-derived mesenchymal stem cells to alleviate hepatic ischemia-reperfusion injury in a receptor-dependent manner. Cell Physiol Biochem 2018;47(2):556–66.
[126] Tauskela JS, Fang H, Hewitt M, et al. Elevated synaptic activity preconditions neurons against an in vitro model of ischemia. J Biol Chem 2008;283(50):34667–76.
[127] Mio Y, Shim YH, Richards E, Bosnjak ZJ, Pagel PS, Bienengraeber M. Xenon preconditioning: the role of prosurvival signaling, mitochondrial permeability transition and bioenergetics in rats. Anesth Analg 2009;108(3):858–66.
[128] Zhang TZ, Zhou J, Jin Q, et al. Protective effects of remifentanil preconditioning on cerebral injury during pump-assisted coronary artery bypass graft. Genet Mol Res 2014;13(3):7658–65.
[129] Loubiere C, Clavel S, Gilleron J, et al. The energy disruptor metformin targets mitochondrial integrity via modification of calcium flux in cancer cells. Sci Rep 2017;7(1):5040.
[130] Kajiwara C, Kusaka Y, Kimura S, et al. Metformin mediates protection against legionella pneumonia through activation of AMPK and mitochondrial reactive oxygen species. J Immunol 2018;200(2):623–31.
[131] Jiang T, Yu JT, Zhu XC, et al. Acute metformin preconditioning confers neuroprotection against focal cerebral ischaemia by pre-activation of AMPK-dependent autophagy. Br J Pharmacol 2014;171(13):3146–57.
[132] Kayser EB, Morgan PG, Sedensky MM. GAS-1: a mitochondrial protein controls sensitivity to volatile anesthetics in the nematode *Caenorhabditis elegans*. Anesthesiology 1999;90(2):545–54.
[133] Quintana A, Morgan PG, Kruse SE, Palmiter RD, Sedensky MM. Altered anesthetic sensitivity of mice lacking Ndufs4, a subunit of mitochondrial complex I. PLoS One 2012;7(8):e42904.
[134] Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. Anesthesiology 2002;96(5):1268–70.
[135] Liljeroth E, Karlsson A, Lagerkranser M, Akeson J. Sustained intravascular exposure to propofol does not prolong pain at the site of injection. Acta Anaesthesiol Scand 2007;51(4):456–9.
[136] Sumi C, Okamoto A, Tanaka H, et al. Propofol induces a metabolic switch to glycolysis and cell death in a mitochondrial electron transport chain-dependent manner. PLoS One 2018;13(2):e0192796.
[137] Krajčová A, Løvsletten NG, Waldauf P, et al. Effects of propofol on cellular bioenergetics in human skeletal muscle cells. Crit Care Med 2018;46(3):e206–12.
[138] Finsterer J, Frank M. Propofol is mitochondrion-toxic and may unmask a mitochondrial disorder. J Child Neurol 2016;31(13):1489–94.
[139] Roshchina VV. New trends and perspectives in the evolution of neurotransmitters in microbial, plant, and animal cells. Adv Exp Med Biol 2016;874:25–77.
[140] Kulma A, Szopa J. Catecholamines are active compounds in plants. Plant Sci 2007;172(3):433–40.
[141] Toyota M, Spencer D, Sawai-Toyota S, et al. Glutamate triggers long-distance, calcium-based plant defense signaling. Science 2018;361(6407):1112–5.
[142] Soto-Burgos J, Bassham DC. SnRK1 activates autophagy via the TOR signaling pathway in *Arabidopsis thaliana*. PLoS One 2017;12(8):e0182591.
[143] Hayashi K, Fujita Y, Ashizawa T, Suzuki F, Nagamura Y, Hayano-Saito Y. Serotonin attenuates biotic stress and leads to lesion browning caused by a hypersensitive response to *Magnaporthe oryzae* penetration in rice. Plant J 2016;85(1):46–56.
[144] Van Alstyne KL, Nelson AV, Vyvyan JR, Cancilla DA. Dopamine functions as an antiherbivore defense in the temperate green alga *Ulvaria obscura*. Oecologia 2006;148(2):304–11.
[145] Grémiaux A, Yokawa K, Mancuso S, Baluška F. Plant anesthesia supports similarities between animals and plants: Claude Bernard's forgotten studies. Plant Signal Behav 2014;9(1):e27886.
[146] Fammartino A, Verdaguer B, Fournier J. Coordinated transcriptional regulation of the divinyl ether biosynthetic genes in tobacco by signal molecules related to defense. Plant Physiol Biochem 2010;48(4):225–31.
[147] Jacobo-Velázquez DA, González-Agüero M, Cisneros-Zevallos L. Cross-talk between signaling pathways: the link between plant secondary metabolite production and wounding stress response. Sci Rep 2015;25(5):8608.
[148] Blume B, Nürnberger T, Nass N, Scheel D. Receptor-mediated increase in cytoplasmic free calcium required for activation of pathogen defense in parsley. Plant Cell 2000;12(8):1425–40.
[149] Wink M. Plant secondary metabolites modulate insect behavior-steps toward addiction? Front Physiol 2018;11(9):364.
[150] Basha SA, Mishra RK, Jha RN, Pandey VB, Singh UP. Effect of berberine and (+/-)-bicuculline isolated from *Corydalis chaerophylla* on spore germination of some fungi. Folia Microbiol (Praha) 2002;47(2):161–5.
[151] Das A, Kamal S, Shakil NA, et al. The root endophyte fungus *Piriformospora indica* leads to early flowering, higher biomass and altered secondary metabolites of the medicinal plant, *Coleus forskohlii*. Plant Signal Behav 2012;7(1):103–12.
[152] Li CF, Zhu Y, Yu Y, et al. Global transcriptome and gene regulation network for secondary metabolite biosynthesis of tea plant (*Camellia sinensis*). BMC Genomics 2015;29(16):560.
[153] Wang Q, Fong R, Mason P, Fox AP, Xie Z. Caffeine accelerates recovery from general anesthesia. J Neurophysiol 2014;111(6):1331–40.
[154] Otmakhov N, Khibnik L, Otmakhova N, et al. Forskolin-induced LTP in the CA1 hippocampal region is NMDA receptor dependent. J Neurophysiol 2004;91(5):1955–62.
[155] Fong R, Wang L, Zacny JP, et al. Caffeine accelerates emergence from isoflurane anesthesia in humans: a randomized, double-blind, crossover study. Anesthesiology 2018;129(5):912–20.
[156] Steppuhn A, Gase K, Krock B, Halitschke R, Baldwin IT. Nicotine's defensive function in nature. PLoS Biol 2004;2(8):E217.
[157] Alkire MT, McReynolds JR, Hahn EL, Trivedi AN. Thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. Anesthesiology 2007;107(2):264–72.
[158] Nakauchi S, Sumikawa K. Endogenously released ACh and exogenous nicotine differentially facilitate long-term potentiation induction in the hippocampal CA1 region of mice. Eur J Neurosci 2012;35(9):1381–95.
[159] Karakaş FP, Şahin G, Türker A. Enhancement of direct shoot regeneration and determination of bioactive secondary metabolites in leaves of *Galega officinalis* L. Turk J Biol 2016;40(6):1311–9.
[160] Colović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol 2013;11(3):315–35.
[161] Meuret P, Backman SB, Bonhomme V, Plourde G, Fiset P. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 2000;93(3):708–17.
[162] Pal D, Dean JG, Liu T, et al. Differential role of prefrontal and parietal cortices in controlling level of consciousness. Curr Biol 2018;28(13):2145–2152.e5.
[163] Olianas MC, Dedoni S, Onali P. Involvement of store-operated Ca(2+) entry in activation of AMP-activated protein kinase and stimulation of glucose uptake by M3 muscarinic acetylcholine receptors in human neuroblastoma cells. Biochim Biophys Acta 2014;1843(12):3004–17.
[164] Ari C, Kovács Z, Murdun C, et al. Nutritional ketosis delays the onset of isoflurane induced anesthesia. BMC Anesthesiol 2018;18(1):85.
[165] Bae HR, Kim DH, Park MH, et al. β-Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. Oncotarget 2016;7(41):66444–54.
[166] Milder JB, Liang LP, Patel M. Acute oxidative stress and systemic Nrf2 activation by the ketogenic diet. Neurobiol Dis 2010;40(1):238–44.
[167] Kenny JD, Taylor NE, Brown EN, Solt K. Dextroamphetamine (but Not Atomoxetine) induces reanimation from general anesthesia: implications for the roles of dopamine and norepinephrine in active emergence. PLoS One 2015;10(7):e0131914.
[168] Taylor NE, Chemali JJ, Brown EN, Solt K. Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology 2013;118(1):30–9.
[169] Zhang LN, Li ZJ, Tong L, et al. Orexin-A facilitates emergence from propofol anesthesia in the rat. Anesth Analg 2012;115(4):789–96.
[170] Rao Y, Liu ZW, Borok E, et al. Prolonged wakefulness induces experience-dependent synaptic plasticity in mouse hypocretin/orexin neurons. J Clin Invest 2007;117(12):4022–33.
[171] Wang TX, Xiong B, Xu W, et al. Activation of parabrachial nucleus glutamatergic neurons accelerates reanimation from sevoflurane anesthesia in mice. Anesthesiology 2018. https://doi.org/10.1097/ALN.0000000000002475. [Epub

ahead of print].
[172] Luo T, Leung LS. Basal forebrain histaminergic transmission modulates electroencephalographic activity and emergence from isoflurane anesthesia. Anesthesiology 2009;111(4):725–33.
[173] Walling SG, Nutt DJ, Lalies MD, Harley CW. Orexin-A infusion in the locus ceruleus triggers norepinephrine (NE) release and NE-induced long-term potentiation in the dentate gyrus. J Neurosci 2004;24(34):7421–6.
[174] Teixeira CM, Rosen ZB, Suri D, et al. Hippocampal 5-HT input regulates memory formation and schaffer collateral excitation. Neuron 2018;98(5):992–1004.e4.
[175] Hambrecht-Wiedbusch VS, Li D, Mashour GA. Paradoxical emergence: administration of subanesthetic ketamine during isoflurane anesthesia induces burst suppression but accelerates recovery. Anesthesiology 2017;126(3):482–94.
[176] Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3(9):537–46.
[177] Jin K, Minami M, Lan JQ, et al. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. Proc Natl Acad Sci U S A. 2001;98(8):4710–5.
[178] Romanko MJ, Rola R, Fike JR, et al. Roles of the mammalian subventricular zone in cell replacement after brain injury. Prog Neurobiol 2004;74(2):77–99.
[179] Fatt M, Hsu K, He L, et al. Metformin acts on two different molecular pathways to enhance adult neural precursor proliferation/self-renewal and differentiation. Stem Cell Rep 2015;5(6):988–95.
[180] Wang J, Gallagher D, DeVito LM, et al. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation. Cell Stem Cell 2012;11(1):23–35.
[181] Liu Y, Tang G, Zhang Z, Wang Y, Yang GY. Metformin promotes focal angiogenesis and neurogenesis in mice following middle cerebral artery occlusion. Neurosci Lett 2014;5(579):46–51.
[182] Dadwal P, Mahmud N, Sinai L, et al. Activating endogenous neural precursor cells using metformin leads to neural repair and functional recovery in a model of childhood brain injury. Stem Cell Rep 2015;5(2):166–73.
[183] Finley J. Alteration of splice site selection in the LMNA gene and inhibition of progerin production via AMPK activation. Med Hypotheses 2014;83(5):580–7.
[184] Finley J. Cellular stress and AMPK activation as a common mechanism of action linking the effects of metformin and diverse compounds that alleviate accelerated aging defects in Hutchinson-Gilford progeria syndrome. Med Hypotheses 2018;118:151–62.
[185] Finley J. Reactivation of latently infected HIV-1 viral reservoirs and correction of aberrant alternative splicing in the LMNA gene via AMPK activation: common mechanism of action linking HIV-1 latency and Hutchinson-Gilford progeria syndrome. Med Hypotheses 2015;85(3):320–32.
[186] Finley J. Oocyte activation and latent HIV-1 reactivation: AMPK as a common mechanism of action linking the beginnings of life and the potential eradication of HIV-1. Med Hypotheses 2016;93:34–47.
[187] Finley J. Transposable elements, placental development, and oocyte activation: cellular stress and AMPK links jumping genes with the creation of human life. Med Hypotheses 2018;118:44–54.
[188] Marinangeli C, Didier S, Ahmed T, et al. AMP-activated protein kinase is essential for the maintenance of energy levels during synaptic activation. iScience 2018;12(9):1–13.
[189] Ferreira AL, Correia R, Vide S, et al. Patterns of hysteresis between induction and emergence of neuroanesthesia are present in spinal and intracranial surgeries. J Neurosurg Anesthesiol 2018. https://doi.org/10.1097/ANA.0000000000000559. [Epub ahead of print].
[190] Sepúlveda 5th PO, Carrasco E, Tapia LF, et al. Evidence of hysteresis in propofol pharmacodynamics. Anaesthesia 2018;73(1):40–8.
[191] http://meetings.aps.org/Meeting/GEC18/Session/PR2.9, [last accessed 12/26/18].
[192] Luo T, Yu S, Cai S, et al. Parabrachial neurons promote behavior and electroencephalographic arousal from general anesthesia. Front Mol Neurosci 2018;4(11):420.
[193] Jones RB, Song H, Xu Y, et al. LINE-1 retrotransposable element DNA accumulates in HIV-1-infected cells. J Virol 2013;87(24):13307–20.
[194] Schmidt A, Bekeschus S. Redox for repair: cold physical plasmas and Nrf2 signaling promoting wound healing. Antioxidants (Basel) 2018;7(10):E146.
[195] Park IJ, Tran QH, Amin ASM, et al. Transient activation of AMP-activated protein kinase at G1/S phase transition is required for control of S phase in NIH3T3 cells. Biochem Biophys Res Commun 2018;504(2):367–73.
[196] Havens CG, Ho A, Yoshioka N, Dowdy SF. Regulation of late G1/S phase transition and APC Cdh1 by reactive oxygen species. Mol Cell Biol 2006 Jun;26(12):4701–11.
[197] Bhasin MK, Denninger JW, Huffman JC, et al. Specific transcriptome changes associated with blood pressure reduction in hypertensive patients after relaxation response training. J Altern Complement Med 2018 May;24(5):486–504.
[198] Zhang Y, Paikari A, Sumazin P, et al. Metformin induces FOXO3-dependent fetal hemoglobin production in human primary erythroid cells. Blood 2018;132(3):321–33.
[199] Liu A, Yang J, Hu Q, et al. Young plasma attenuates age-dependent liver ischemia reperfusion injury. FASEB J 2018. https://doi.org/10.1096/fj.201801234R. fj201801234R [Epub ahead of print].
[200] Pirotte N, Stevens AS, Fraguas, et al. Reactive oxygen species in planarian regeneration: an upstream necessity for correct patterning and brain formation. Oxid Med Cell Longev 2015;2015:392476.
[201] Lei K, Thi-Kim VuH, Mohan RD, et al. Egf signaling directs neoblast repopulation by regulating asymmetric cell division in planarians. Dev Cell 2016;38(4):413–29.
[202] Ratner HK, Sampson TR, Weiss DS. I can see CRISPR now, even when phage are gone: a view on alternative CRISPR-Cas functions from the prokaryotic envelope. Curr Opin Infect Dis 2015;28(3):267–74.