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Intermittent metabolic switching, neuroplasticity and brain health

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Abstract

During evolution, individuals whose brains and bodies functioned well in a fasted state were successful in acquiring food, enabling their survival and reproduction. With fasting and extended exercise, liver glycogen stores are depleted and ketones are produced from adipose-cell-derived fatty acids. This metabolic switch in cellular fuel source is accompanied by cellular and molecular adaptations of neural networks in the brain that enhance their functionality and bolster their resistance to stress, injury and disease. Here, we consider how intermittent metabolic switching, repeating cycles of a metabolic challenge that induces ketosis (fasting and/or exercise) followed by a recovery period (eating, resting and sleeping), may optimize brain function and resilience throughout the lifespan, with a focus on the neuronal circuits involved in cognition and mood. Such metabolic switching impacts multiple signalling pathways that promote neuroplasticity and resistance of the brain to injury and disease.

Food scarcity has been a driving force for the evolution of nervous systems; indeed, even the most advanced capabilities of the human brain (imagination, creativity and language) arose via selection for individuals who were adept at cooperating to acquire and share food[1–3]. However, people in modern societies typically consume food three or more times each day. Every time they eat, the glycogen stores in their liver are replenished; liver glycogen provides 700–900 calories of glucose or energy, an amount that will last 10–14 hours in individuals who are not exercising. Subsequently, liver energy stores are depleted, circulating glucose levels remain low and adipose cells release fatty acids, which are converted in the liver to the ketone bodies β-hydroxybutyrate (BHB) and acetoacetate

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(AcAc), which are released into the blood and are used as energy substrates by neurons[4,5] (FIG. 1). The transition from utilization of carbohydrates and glucose to fatty acids and ketones as the major cellular fuel source can be referred to as the 'G-to-K switch'. Upon consumption of food after a fast, the major energy source for cells switches back to glucose ('K-to-G switch'). Because exercise accelerates the depletion of liver glycogen stores, it hastens the onset of the G-to-K switch. For example, the metabolic switch may occur in someone who runs for 1 hour (during which time they use approximately 600 calories) beginning 4 hours after their most recent meal.

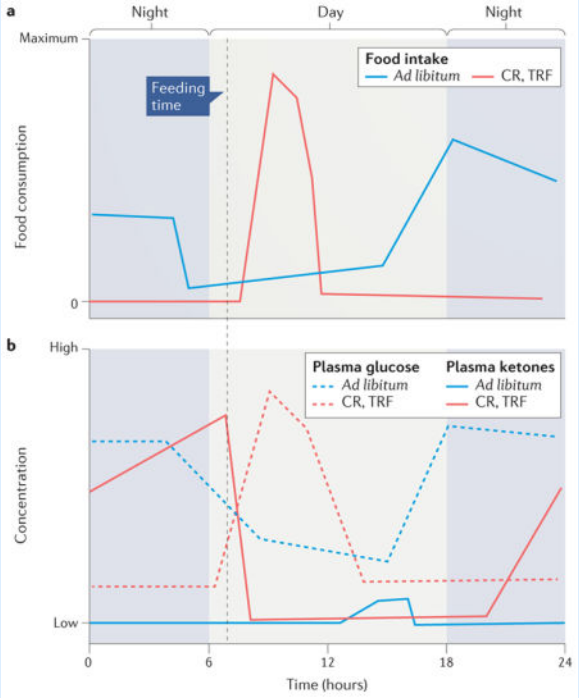
Beyond the switch in the major cellular fuel source, emerging findings are revealing remarkably complex and coordinated adaptations of the brain and body that enable the individual to maintain and even enhance their cognitive and physical performance for extended time periods in the fasted state[6,7]. In general, signalling pathways engaged when the G-to-K switch occurs serve to bolster cellular stress resistance and set the stage for subsequent cellular structural and functional plasticity that occurs after the K-to-G switch. We define intermittent metabolic switching (IMS) as scenarios in which an individual's eating and exercise patterns result in periodic G-to-K switches. The most commonly employed IMS protocols in animals involve intermittent fasting (IF), including alternate-day fasting (ADF) and daily time-restricted feeding (TRF), and are described in BOX 1. Studies of animals and humans are revealing beneficial effects of IF on health beyond those resulting from caloric restriction (CR) without IMS[8–11]. Here, we review the molecular and cellular adaptations of neurons to IMS from the perspectives of brain evolution, neuroplasticity and resistance of the nervous system to injury and disease. We focus on brain regions involved in cognition, mood regulation and motor control; for those interested in the hypothalamus and neuroendocrine regulation of feeding behaviour and circadian rhythms, we refer readers to recent review articles[12,13].

Box 1

Animal models of intermittent metabolic switching

Alternate-day fasting (ADF) and daily time-restricted feeding (TRF) are the most widely employed intermittent fasting (IF) approaches for controlled frequent intermittent metabolic switching (IMS) in mice and rats. In ADF, the animals are deprived of food for 24 hours every other day[8]. For daily TRF, there are two different protocols: 1) animals are deprived of food for a specific time period each day (for example, 16 hours)[9], and 2) animals are provided a daily allocation of an amount of food that is 30–40% less than their *ad libitum* consumption (that is, caloric restriction (CR)), in which case they typically consume all their food within 2 4 hours of their feeding time[184–186]. The figure shows depictions of food intake in rats or mice on 30–40% CR (TRF) during a 24-hour period (panel a) and the corresponding changes in plasma ketone and glucose concentrations (panel b; solid lines are ketone concentrations and dashed lines are glucose concentration). Animals on the CR diets consume all their daily food allotment within a 4 hour time window and therefore fast for 20 hours; during the last half of the fasting period, plasma ketone concentrations are elevated and the plasma glucose concentration remains low. The illustrations are based on data in several different studies,

including those in REFS 184–187. Although plasma β-hydroxybutyrate levels are rarely measured in exercise studies, there are data showing that bouts of vigorous exercise (running or swimming) do elevate circulating ketone levels in rodents[188,189].



We suggest that switching between time periods of negative energy balance (short fasts and/or exercise) and positive energy balance (eating and resting) can optimize general health and brain health. Illustrative of the sustained health benefits of IMS are enhanced insulin sensitivity, reduced abdominal fat, maintenance of muscle mass and reduced resting heart rate and blood pressure[7]. It is important to note that the short-term IF discussed herein is in contrast with long-term fasts of a week or more, which may have detrimental effects on muscle mass. Because sedentary, overindulgent lifestyles can increase the risk of several neurodegenerative and psychiatric disorders (see section on IMS and neurological disorders below), a better understanding of the neurobiology of IMS may lead to new approaches for improving brain health throughout the life course.

Neuronal adaptations to IMS

Behavioural adaptations

Experimental evidence supports the evolutionary principle that the brain and body perform at high levels in environments that demand IMS. Because many studies that have evaluated the effects of IF and exercise on cognition and mood did not include measurements of circulating ketones, we describe here only a few examples that either included ketone measurements or employed IF protocols known to involve IMS. Thirty years ago, Ingram *et al.* reported that mice maintained on a daily TRF schedule (40% CR; see BOX 1) beginning at weaning age exhibit no age-related learning and memory impairment and improved

locomotor performance in middle and old age compared with control mice fed *ad libitum*[14]. When fasting was initiated in 14-month-old mice, their spatial navigation, working memory, strength and coordination at 22–25 months of age were superior to those of control mice fed *ad libitum*. Whereas mice fed *ad libitum* develop age-related hippocampus-dependent spatial learning and memory deficits, mice maintained on daily TRF (40% CR) during their adult life do not experience a decrement in cognition[15]. Daily TRF also ameliorates age-related anxiety-like behaviours in mice[16]. Middle-aged mice fed a very-low-calorie diet for 4 consecutive days every other week (during which ketones were elevated) for 7 months exhibited significantly better spatial learning and memory in the Barnes maze, and significantly higher recognition and working memory in the novel object recognition task and Y-maze, than mice continuously fed *ad libitum*[17].

Evidence from human and animal studies has established that regular aerobic exercise can improve cognitive performance and can protect against anxiety and depression[18,19]. Cognitive challenges performed during exercise result in levels of enhancement of synaptic plasticity, as well as learning and memory, greater than either challenge alone[20]. However, in most studies of effects of exercise on the brain, ketone levels are not measured; therefore, it is not known whether IMS occurs. Nevertheless, from an evolutionary perspective, it is noteworthy that precise navigational decision-making (cognitive challenge) while rapidly traversing the landscape (running) in a food-deprived and/or fasted state would be critical for survival. Indeed, combining exercise with cognitive challenges and/or IF results in improvements in neuroplasticity and cognitive performance superior to those from the individual challenges alone[21,22].

Neuronal network activity, synaptic plasticity and neurogenesis

Hippocrates wrote more than 2,400 years ago that fasting can prevent or lessen the severity of epilepsy, a disorder he called “the sacred disease” (REF. 23). During the past 50 years, it was established that ketones can constrain neuronal network activity and ketogenic diets can benefit many patients with epilepsy[24]. More recently, it was shown that rats maintained on ADF exhibit resistance to seizure-induced hippocampal damage and associated cognitive impairment[25] and that IF can reduce seizure frequency in children who do not fully respond to a ketogenic diet[26].

Although IMS elicited by IF and/or regular vigorous exercise can protect neuronal circuits against aberrant hyperexcitability, IMS also enhances structural and functional synaptic plasticity. Long-term potentiation (LTP) is an enduring activity-dependent increase in synaptic strength that occurs in response to repetitive stimulation of synapses and is believed to be a common cellular manifestation of learning and memory. Rats or mice that run or are fasted intermittently exhibit enhanced LTP at hippocampal synapses compared with sedentary animals fed *ad libitum*[27–29]. Daily TRF (22 hours of fasting every day) for 3 weeks improves performance in the Barnes maze test and increases dendritic spine density and LTP in CA1 neurons in rats[30]. IMS can also prevent age-related deficits in LTP[31,32]. IMS regimens involving daily TRF (30% CR) alone, or in combination with running-wheel exercise, result in increased dendritic spine density in hippocampal dentate granule neurons in wild-type mice and in hyperphagic diabetic mice[21]. The latter study demonstrated

additive effects of dietary energy restriction and running on dentate neuron dendritic spine density, consistent with the notion that synaptic plasticity can be optimized by combining exercise with energy restriction.

New neurons are born continuously throughout adult life in the hippocampal dentate gyrus of mammals, including rodents, monkeys and humans. The newly generated neurons differentiate into granule neurons and receive synaptic inputs from other granule neurons, interneurons and neurons in the entorhinal cortex, basal forebrain (including the septum) and mammillary bodies[33]. Both running and IF can enhance neurogenesis, with running stimulating the proliferation of the stem cells[33] and IF increasing the survival of the newly generated neurons[34]. Running also strengthens inputs of newly generated neurons from brain regions critical for spatial learning and memory, including the entorhinal cortex and basal forebrain (including the septum)[35]. However, the roles of the G-to-K switch in the effects of running and IF on neurogenesis remain to be determined.

Signalling pathways impacted by IMS

Neurotransmitters and neurotrophic factors

Glutamate is the major excitatory neurotransmitter in the CNS and, as such, is essential for all behaviours, including learning and memory, emotional responses, sensory input and integration and motor system activity. Glutamate receptor activation triggers Ca^{2+} influx into the post-synaptic neuron, which engages downstream pathways that mediate adaptive structural (dendritic spine growth and synaptogenesis) and functional (LTP and long-term depression) responses of neuronal circuits to environmental challenges. The downstream pathways involve Ca^{2+}-responsive kinases such as calcium/calmodulin-dependent kinases and protein kinase C as well as transcription factors such as cAMP-responsive element-binding protein (CREB) and nuclear factor-κB (NF-κB)[36,37]. In rats, 18 hours of fasting results in CREB activation in hippocampal and entorhinal cortex neurons[38]. Running-wheel exercise also triggers upregulation of CREB in hippocampal and cerebral cortical cells in mice[39]. This pathway is highly conserved because fasting enhances long-term memory formation in multiple tasks in *Drosophila melanogaster* by a mechanism requiring CREB activation in mushroom body neurons[40]. Ketones, particularly BHB, upregulate GABAergic tone, which can protect against seizures[41,42], and may mediate adaptive responses of neuronal circuits to IMS. The monoamine neurotransmitters serotonin, noradrenaline and dopamine may also play important roles in the effects of IMS on neuronal network activity[43,44].

A robust and readily discernible effect of IMS on a neurotransmitter system involves brainstem cholinergic neurons that innervate the heart. Endurance athletes exhibit low resting heart rates and blood pressure and high heart rate variability (HRV; the variation in time intervals between individual heartbeats) as a result of increased activity of the brainstem cardiovagal neurons[45]. Similar enhancement of parasympathetic tone and consequent reductions in resting heart rate and blood pressure, and increased HRV, occur in response to ADF or daily TRF[46,47]. Recordings of cardiovagal neuronal activity in brain-derived neurotrophic factor (BDNF) heterozygous knockout mice suggest that BDNF mediates the enhancement of parasympathetic tone in response to IMS[48].

BDNF plays pivotal roles in synaptic plasticity (synaptogenesis and LTP), neurogenesis and neuronal stress resistance[49]. BDNF likely plays important roles in behavioural and neuronal network adaptations to IMS because BDNF expression in cells in multiple regions is induced by running and IF[49], and ablation of TrkB tyrosine kinase (also known as BDNF/NT3 growth factor receptor (NTRK2)) in hippocampal neural stem cells abolishes the ability of IMS to enhance neuroplasticity[50]. Insulin-like growth factor 1 (IGF1) signalling is also upregulated in response to IMS as demonstrated in studies of the effects of ketogenic diets, exercise and CR and/or IF on brain IGF1 signalling[51–53]. Two recent studies showed that BHB induces BDNF expression in hippocampal and cortical neurons in cell culture and *in vivo*[54,55], suggesting that BHB is itself a signal that 'alerts' neurons in the brain that the metabolic switch has occurred.

Fibroblast growth factor 2 (FGF2) plays important roles in stimulating neural stem cell proliferation and regulating neurite outgrowth and cell survival during brain development[56]. FGF2 can also protect neurons against excitotoxic, metabolic and oxidative stress by mechanisms involving enhancement of cellular Ca^{2+} homeostasis and upregulation of antioxidant enzymes[57,58]. FGF2 levels increase in the cerebral cortex and striatum of mice in response to ADF[59] and in the hippocampus in response to running-wheel exercise[60]. The formation and extinction of memories of fearful events have been reported to be mediated, in part, by FGF2, suggesting a role for FGF2 in the critical synaptic plasticity required for survival during periods of food scarcity[61]. However, whether and to what extent FGF2 signalling is critical for the enhancement of cognition, synaptic plasticity and neurogenesis by IMS remains to be determined.

Mitochondrial biogenesis and cellular stress-resistance pathways

In response to intermittent bouts of exercise, the number of well-functioning mitochondria in muscle cells increases in a process called mitochondrial biogenesis, which is mediated by reactive oxygen species (ROS), Ca^{2+}/calmodulin-dependent protein kinase type IIγ (CaMKII), AMP kinase (AMPK; also known as 5′-activated protein kinase (PRKAA)) and NAD-dependent lysine deacetylase sirtuin 1 (SIRT1) and the transcription factor peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α; also known as PPARGC1A)[62–64] (FIG. 2). Emerging findings suggest that IMS stimulates mitochondrial biogenesis in neurons and that such mitochondrial biogenesis enables synaptic plasticity. When mitochondrial biogenesis is inhibited by knockdown of PGC-1α in developing hippocampal neurons, basal synapse formation is reduced and the ability of BDNF to induce synaptogenesis is abolished[65]. PGC1α is also essential for the long-term maintenance of dendritic spines of hippocampal dentate granule neurons in adult mice[65]. Because BDNF expression is upreg-ulated in response to the G-to-K switch and BHB[54,55], BDNF signalling may stimulate mitochondrial biogenesis to provide the increased numbers of mitochondria required to support the function of newly formed and potentiated synapses (FIG. 2). Interestingly, PGC1α can enhance BDNF expression[66], suggesting a positive feedback signalling mechanism whereby BDNF induces PGC1α and vice versa. The increased activity in neuronal circuits that occurs during exercise and fasting may also contribute to mitochondrial biogenesis via a Ca^{2+}–CaMKII–CREB–PGC1α pathway[6,67].

The metabolic efficiency and stress tolerance of neuronal mitochondria can be enhanced by IMS. To illustrate this point, we highlight the mitochondrial NAD^+-dependent protein deacetylase SIRT3, which is emerging as a key mediator of adaptive responses of neurons to bioenergetic challenges[68]. SIRT3 expression is upregulated in the cerebral cortical and hippocampal neurons of mice in response to running-wheel exercise by a mechanism requiring activation of NMDA glutamate receptors[69]. Deletion of SIRT3 from neurons renders them vulnerable to excitotoxicity and mitochondrial stress, whereas overexpression of SIRT3 is neuroprotective[69]. SIRT3-mediated deacetylation of proteins in the electron transport chain and tricarboxylic acid (TCA) cycle may enhance the efficiency of mitochondrial ATP production, whereas deacetylation of superoxide dismutase 2 reduces mitochondrial oxidative stress and deacetylation of cyclophilin D protects neurons against apoptosis[69,70] (FIG. 2).

Mammalian target of rapamycin and autophagy

A highly conserved pathway by which cells regulate protein synthesis in response to fluctuations in nutrient availability (principally glucose and amino acids) involves a protein called mechanistic target of rapamycin (mTOR; also known as serine/threonine-protein kinase mTOR (MTOR) and mammalian target of rapamycin)[71,72]. In the fed state, activation of mTOR by upstream nutrient-sensing proteins activates ribosomal protein S6 kinase to increase general protein synthesis and activates sterol regulatory element-binding protein (SREBP1; also known as SREBF1) to increase lipid synthesis. Conversely, during fasting and extended exercise, when the metabolic switch is on, mTOR activity decreases. In essence, cells are in a ‘growth mode’ when mTOR is active and in a ‘conserve-resources mode’ when the mTOR pathway is inactive. During fasting and sustained exercise, the mTOR pathway is inhibited and autophagy is stimulated in a wide range of tissues, including those in the nervous system[73,74]. The metabolic shift to ketogenesis not only is associated with the conserve-resources mode of cells but may also be causally involved because BHB can stimulate autophagy[75]. Indeed, fasting or treatment of animals with the mTOR inhibitor rapamycin can extend lifespan and healthspan in several different organisms, including mice[7,76]. Conversely, lack of IMS may impair autophagy and increase the risk of neurodegenerative disorders[77,78].

Autophagy is upregulated in cerebral cortical and cerebellar neurons in response to fasting[73], and genetic and pharmacological manipulations of mTOR and autophagy alter synaptic plasticity and neurogenesis in ways consistent with the involvement of these pathways in neuronal network adaptations to IMS[73]. mTOR mediates the local synthesis of proteins in dendrites that is required for long-term changes in synaptic strength that are believed to be critical for learning and memory[79–81], and mTOR is also involved in some forms of synaptic plasticity[82–84]. Because IF and exercise enhance synaptic plasticity and cognition, it will be important to establish the specific contributions of the regulation of mTOR and autophagy pathways to the underlying structural and functional adaptations of neuronal networks to IMS.

AMPK is a cellular energy status responsive enzyme (activated when the ratio of ATP to AMP and/or ADPdecreases) that mediates the downregulation of mTOR and upregulation of

autophagy in response to fasting and vigorous exercise in muscle cells[85,86]. Recent findings suggest that AMPK also mediates adaptive responses of neuronal networks to IMS. Daily treadmill training in rats results in activation of AMPK in hippocampal cells[87], and pharmacological inhibition of AMPK enhances contextual fear memory in mice[88]. AMPK activity is increased in response to fasting and is required for fasting-induced dendritic spine formation and synaptic functional plasticity in hypothalamic arcuate nucleus neurons[89]. Mice treated with an AMPK agonist exhibit enhanced cognition and motor system function, consistent with roles for AMPK in the beneficial effects of IMS on neuroplasticity[90]. Although intermittent AMPK activation resulting from physiological bioenergetic challenges can enhance neuroplasticity, sustained AMPK activation can impair axonal and dendritic plasticity[91], consistent with the importance of a recovery period for optimal neuroplasticity (FIG. 3).

IMS-associated peripheral signals

Multiple neuroactive signalling molecules are released into the blood from peripheral organs in response to the G-to-K metabolic switch. The ‘hunger hormone’ ghrelin is among the most intensively studied of such signals because of its effects on hypothalamic regulation of food intake. Ghrelin is produced in a subpopulation of cells in the gut from which it is released into the blood in response to fasting, whereas food intake inhibits its release. Ghrelin and the additional peripheral signals generated when the metabolic switch is on also affect the plasticity and resilience of neuronal circuits throughout the brain, including those involved in motivation and cognition[92,93]. Ghrelin enhances hippocampal synaptic plasticity, neurogenesis and hippocampus-dependent learning and memory by direct actions on hippocampal cells and by stimulating serotonergic neurons in the brainstem raphe nucleus, which innervate the hippocampus[94]. Ghrelin can also have an anxiolytic effect on mice[95]. However, it is unclear whether ghrelin mediates the beneficial effects of IMS on neuroplasticity and behaviour.

Several proteins released from skeletal muscle during exercise, so-called myokines, may contribute to the CNS adaptations associated with IMS[27]. Interleukin 6 (IL-6) is best known as a mediator of immune cell responses to infectious agents and tissue damage, but IL-6 is also produced in and released from muscle cells in response to vigorous exercise and fasting and increases the insulin sensitivity of muscle cells[96,97]. Studies of IL-6-knockout mice have revealed important roles for IL-6 in CNS neuroplasticity, including regulation of hippocampus-dependent learning and memory[98]. Insulin-like growth factor I (IGF1) and fibroblast growth factor 2 (FGF2) are two neurotrophic factors that can enhance neuroplasticity and protect neurons against metabolic and oxidative stress[99,100]. IGF1 and FGF2 are produced by neurons and astrocytes but are also myokines produced in response to fasting and exercise[101,102]. Although the effects of circulating FGF2 on neuroplasticity are unclear, studies in which circulating IGF1 is selectively neutralized suggest an important role for peripheral-organ-derived IGF1 in the beneficial effects of IMS on brain neuroplasticity. Running stimulates IGF1 transport from the blood into neurons in the brain, and this uptake is associated with running-induced increases of neuronal network activity and BDNF expression[103]. Neutralization of circulating IGF1 blocks the abilities of exercise to modulate hippocampal neuronal network activity and protect neurons against excito-

toxicity[104]. Nevertheless, the involvement of peripheral-organ-derived IGF1 in the beneficial effects of metabolic switching on the brain is complex because although exercise increases circulating IGF1 levels, fasting reduces circulating IGF1 levels by reducing production of IGF1 in the liver. However, similar to the prominent decrease in circulating insulin levels and the associated increase in sensitivity of insulin receptors to insulin in response to IMS, it is possible that fasting increases the sensitivity of the IGF1 receptor signalling pathway to IGF1.

Originally touted for its ability to 'brown' white fat, thereby increasing its thermogenic potential, the protein irisin is released from muscle cells in response to exercise and has been reported to enter the brain and upregulate BDNF expression[66]. However, it remains to be determined whether irisin is particularly important in the enhancement of neuroplasticity and stress resistance conferred by IMS. A recent study provided evidence that the enzyme cathepsin B is an exercise-induced peripheral signal that contributes to the cognitive benefits of exercise[105]. Best known for its role as a lysosomal protease, plasma cathepsin B levels are increased in response to exercise in mice, monkeys and humans, and circulating cathepsin B levels are positively correlated with aerobic fitness and recall memory in humans[105]. Hippocampus-dependent spatial memory is impaired in cathepsin-B-deficient mice, and these mice also lack the normal exercise-induced enhancement of hippocampal neurogenesis and spatial memory[105]. The mechanism by which exercise induces cathepsin B release from muscle cells is unknown, but it might involve stimulation of autophagic flux.

Emerging findings are revealing that BHB regulates neuronal gene transcription in ways that promote synaptic plasticity and cellular stress resistance. BHB induces the expression of BDNF in cultured cerebral cortical neurons, an effect that occurs only when glucose levels are fairly low[62]. Running-wheel exercise increases circulating BHB levels in mice, and intraventricular infusion of BHB induces *Bdnf* gene transcription in hippocampal cells[55]. BHB may induce *Bdnf* gene transcription by inhibiting histone deacetylases (HDACs) that normally repress *Bdnf* expression[55,106]. Given that CR, fasting and exogenous ketone supplementation increase histone acetylation in peripheral mouse tissue and that exercise decreases histone deacetylation in the hippocampus, it is likely that the inhibitory effects of ketones on HDACs are amplified when exercise occurs in the fasted state[107]. In addition, via actions in the mitochondria, BHB triggers the activation of the cytoplasmic transcription factor NF-κB in neurons, which then translocates to the nucleus and induces *Bdnf* expression[54]. Such findings suggest that BHB is not only a biomarker of the metabolic switch and an energy source for neurons but is also a peripheral signal that activates neuronal signalling pathways that enhance synaptic plasticity, cognition and neuronal stress resistance. Indeed, it was reported that oral administration of a BHB ester to rats for 5 days improves their spatial learning and memory and enhances their endurance in a treadmill test[108]. In addition to their roles as energy substrates and signalling molecules, BHB and AcAc are also precursors to membrane lipids in brain cells, including neurons and, notably, the oligodendrocytes[109], suggesting a benefit of IMS for axonal myelination.

IMS and acute CNS injury

Epilepsy, stroke and traumatic brain and spinal cord injury are major causes of morbidity throughout the world. Excitotoxicity, metabolic failure and oxidative stress play prominent roles in these acute neurological insults[110]. Rats maintained on IF for several months before exposure to the seizure-inducing excitotoxin kainate exhibit reduced loss of hippocampal pyramidal neurons and improved performance in a hippocampus-dependent water maze test of spatial learning and memory compared with rats fed *ad libitum*[25]. A daily IF and/or CR diet that elevates circulating BHB levels also suppresses seizures in a genetic mouse model of epilepsy[111]. In models of focal ischaemic stroke, rats or mice maintained on IF (ADF) prior to cerebral vessel occlusion exhibit reduced death of cerebral cortical neurons and improved functional outcomes[59,112]. Compared with rats fed *ad libitum*, rats maintained on daily TRF (40% CR) beginning 3 months before, and continuing for 70 days after, global cerebral ischaemia exhibited recovery of spatial memory deficits[113]. IF initiated either before or after a contusion injury to the thoracic spinal cord significantly improves recovery of motor function in rats[114], and similar beneficial effects of IF following injury are evident in a rat model of incomplete cervical spinal cord injury[115]. A single 24 hour fast following injury lessens brain damage and ameliorates cognitive deficits in a rat model of traumatic brain injury[116]. These findings demonstrate that IMS can protect neurons and enhance resilience following injury. In light of the lack of any effective drugs for acute CNS injury, it would seem prudent to evaluate IF interventions in randomized controlled trials in human patients who have suffered a stroke or traumatic CNS injury.

With regards to cellular and molecular mechanisms, IF upregulates pathways involved in resistance to proteotoxic stress, neurotrophic factor signalling, DNA repair, mitochondrial metabolism and bioenergetics, antioxidant defences and Ca^{2+} buffering and downregulates pro-inflammatory cytokines[117–123]. Targeted analyses of proteins in pathways of interest have revealed that IF upregulates expression of the protein chaperones heat shock 70-kilodalton protein (HSP70; also known as HSPA) and 78-kilodalton glucose-regulated protein (HSPA5; also known as GRP78), the antioxidant enzyme haem oxygenase 1 and the neurotrophic factors BDNF and FGF2. IF reduces levels of pro-inflammatory cytokines (tumour necrosis factor (TNF), IL-1β and IL-6) in the uninjured brain and in ischaemic brain tissue in a mouse model of focal ischaemic stroke[59]. Similar to IF, exercise upregulates neurotrophic signalling and suppresses neuroinflammation[120]. The contribution of ketosis to the excitoprotective effects of IMS has not been established but could be tested in animal models in which ketone production or transport into neurons is genetically or pharmacologically disabled. Ketones may also mediate neuronal resistance to ischaemic and traumatic insults, as demonstrated in animal models in which BHB treatment lessened brain damage by mechanisms involving enhanced mitochondrial bioenergetics and stress resistance as well as suppression of neuroinflammation[124–126]. Indeed, BHB exerts anti-inflammatory actions by activating hydroxy-carboxylic acid receptor 2 and inhibiting the NRLP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome[127].

IMS and neurological disorders

Alzheimer disease (AD) and Parkinson disease (PD) are the two most common neurodegenerative disorders[128,129]. The major risk factor for both diseases is age, with symptom onset typically occurring in people older than 70 years of age. The number of elderly individuals afflicted with AD or PD is rising rapidly because life expectancy has increased as a result of medical advances that enable those who would have previously died at a younger age from cardiovascular disease, cancer or diabetes to live beyond the age of 70 years[130]. Because there are no treatments that impact the disease progression in patients with AD or PD, lifelong diet and lifestyle interventions that retard ageing processes and thereby reduce disease risk may be of great value. In laboratory animals, IF (daily TRF or ADF) extends the average lifespan by up to 40% and protects against major chronic diseases, including cancer, diabetes and kidney disease[7]. Increasing evidence suggests that individuals with sedentary, overindulgent lifestyles are at increased risk of developing AD and PD, and animal studies support the notion that a chronic positive energy balance devoid of IMS renders the brain prone to AD and PD[131,132]. Conversely, exercise and moderation of energy intake reduce the risk of AD and PD[133,134], and exercise intervention trials further suggest that IMS reduces clinical symptoms in many patients with AD and PD[135,136].

The identification of genetic mutations that cause early-onset AD enabled the generation of transgenic mouse models that manifest some features of AD, including β-amyloid (Aβ) plaque and neurofibrillary tangle-like pathologies and cognitive impairment. Several studies have demonstrated that IMS regimens can counteract neuropathological and behavioural features in AD mouse models. For example, daily TRF (30% or 40% CR) reduced the accumulation of Aβ plaques in *App*-mutant mice[137,138], and long-term (1-year) IF (ADF) and daily TRF prevented the development of cognitive impairment in 3xTg-AD mice that express beta-amyloid precursor protein (APP), presenilin 1 and tau mutations[139]. Interestingly, in the latter study, daily TRF lessened Aβ and tau pathologies, whereas ADF did not, suggesting that ADF protects neurons against synaptic dysfunction and cognitive deficits despite the presence of pathological Aβ and tau. As reviewed recently, aerobic exercise regimens counteract Aβ pathology and improve cognition in AD mouse models[140].

Mechanisms by which IMS may lessen neuropathology and ameliorate cognitive deficits in AD mice include a reduction of amyloidogenic enzymatic processing of APP, suppression of inflammation, constraint of neuronal hyperexcitability and upregulation of adaptive neuronal stress-resistance pathways (for example, neurotrophic factors, antioxidant defences and nuclear and mitochondrial sirtuins)[6,141,142]. Ketones may counteract AD pathogenesis because a ketone ester diet that elevates BHB more than tenfold lessens Aβ and tau pathologies and ameliorates behavioural abnormalities in 3xTg-AD mice[143]. Moreover, Castellano *et al.* recently reported that a 3-month aerobic training (brisk walking) programme increased brain cell ketone utilization in patients with AD threefold without affecting cerebral glucose utilization[144], which may be one reason that aerobic exercise can protect the brain against AD. That IF may be another approach for subjects at risk of or with AD is suggested by a study using ^{11}C-acetoacetate positron emission tomography (PET) imaging that showed that within 48 hours of the onset of fasting, there is a sevenfold to eightfold increase in brain uptake of ketones[4,145]. Moreover, whereas brain cell uptake of

glucose is severely impaired in patients with AD, the cells remain capable of utilizing ketones[146].

Selective degeneration of nigrostriatal dopaminergic neurons, similar to that occurring in PD, can be induced by administration of mitochondrial toxins that selectively accumulate in dopaminergic neurons. When mice are maintained on an ADF IMS regimen before neurotoxin administration, their dopaminergic neurons are relatively resistant to degeneration and their motor deficits are reduced compared with mice fed *ad libitum*[147]. Daily TRF (30% CR) was also effective in reducing motor deficits and attenuating dopamine depletion in a unilateral 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion rhesus macaque PD model[148]. Intermittent treadmill exercise is also beneficial in protecting dopaminergic neurons and promoting functional recovery in MPTP PD models[149]. Compared with neurotoxin models, the impact of IMS on neuropathology and functional deficits in transgenic PD animal models is largely unexplored. Transgenic mice expressing a mutant form of α-synuclein (A53T) that causes familial PD exhibit age-dependent accumulation of α-synuclein inclusions in neurons throughout the neuraxis develop progressive autonomic nervous system and motor dysfunction and die before they reach 1 year of age. Autonomic dysfunction in these mice is ameliorated by ADF and exacerbated by excessive caloric intake[150]. Enhancing neurotrophic support (BDNF and glial-cell-line-derived neurotrophic factor), induction of protein chaperones, ketogenesis and ghrelin signalling are among the neuroprotective mechanisms of action of IMS suggested from the experiments with PD animal models[151–153].

Depression and anxiety disorders are major causes of morbidity, and their incidence has increased in parallel with increases in obesity and diabetes in many countries[154]. Data from human and animal studies suggest that sedentary, overindulgent lifestyles increase the risk of anxiety disorders and depression[155] and that IMS effected by exercise or IF can improve mood and ameliorate anxiety and depression[156–159]. The ability of exercise to ameliorate symptoms of depression and anxiety is well known, and the underlying mechanisms have been elucidated, with upregulation of BDNF expression in neuronal circuits that regulate mood playing a role[160–162]. Increased activity within hippocampal and frontal cortical networks and enhanced noradrenergic input to those neurons may mediate upregulation of BDNF expression via activation of CREB by Ca^{2+}-dependent and cAMP-dependent pathways[163,164]. Considerable evidence also suggests that BDNF signalling mediates the anxiolytic and antidepressant actions of the most commonly prescribed antidepressant drugs (serotonin and noradrenaline reuptake inhibitors). Interestingly, selective ablation of the BDNF receptor TrkB in hippocampal neural stem cells abolishes the abilities of wheel running and anti-depressant drugs to ameliorate anxiety and depression in mice[165]. The recent finding that BHB induces BDNF expression in hippocampal and cortical neurons[54,55] suggests that ketones mediate the antidepressant effects of exercise and IF. Anxiolytic and antidepressant effects of IGF1 are suggested by data showing that peripheral administration of IGF1 exerts antidepressant actions, whereas peripheral IGF1-neutralizing antibodies attenuate the antidepressant effects of exercise in mice[166,167]. Similar experiments have not yet been performed to determine whether IGF1 also plays a role in the anxiolytic and antidepressant effects of IF.

During the past 3 decades, there has been a rapid increase in the number of children diagnosed with an autism spectrum disorder (ASD), which manifests, to varying extents, in social communication and language deficits, anxiety and repetitive behaviours[168,169]. The increase in autism tracks remarkably closely with the increase in childhood overweight or obesity during the same time period (data from autismspeaks.org and the US Centers for Disease Control), suggesting a causal link between lack of metabolic switching and autistic behaviours. In support of the latter possibility are data showing that nearly twice as many children diagnosed with ASD are overweight or obese as control children[170]. The underlying neurobiological mechanisms may include reduced BDNF expression and excessive mTOR pathway activation. Indeed, human adolescents with BDNF haploinsufficiency score higher on an autism clinical rating scale than age-matched control subjects[171], and mTOR is hyperactivated in animal models of ASDs, which may result in aberrant dendritic spinogenesis and dysregulation of neuronal network activity[172]. Consistent with a potential benefit of IMS in ASD, exercise is effective in reducing behavioural issues in many children with ASD[173]. In the BTBR mouse model of ASD, a ketogenic diet improved symptoms by increasing sociability and decreasing self-directed repetitive behaviour[174]. It was recently reported that a ketogenic diet also improves symptoms in children with ASD[175]. As yet, trials of IF in ASD have not been performed.

IMS and optimization of brain health

It has become clear that sedentary overindulgent lifestyles in which IMS is lacking preclude optimal brain health. The rapid increase in overweight and obese individuals, including children, during the past 40 years is contributing to an emerging ‘epidemic’ of cognitive impairment and dementia that will intensify in coming decades. As reviewed elsewhere, evidence supporting the latter two statements is strong, and the mechanisms by which lack of IMS adversely affects neuroplasticity and risk of major brain disorders are becoming understood[176,177]. When rodents are maintained on an obesogenic diet (high fat and sugar) or are genetically defective in leptin signalling and therefore eat excessively, they perform more poorly on learning and memory tests than nonobese control animals[178–180]. Studies of the hippocampus have shown that deleterious effects of obesity on cognition involve impaired synaptic plasticity and neurogenesis, reduced expression of BDNF and local neuroinflammation[176–180]. IMS, triggered with running-wheel exercise and/or IF, can counteract the adverse effects of excessive energy intake on hippocampal plasticity[6]. Although a chronic positive energy balance is not optimal for brain health and may increase the risk of neurological disorders, including anxiety, depression, AD and PD, a chronic negative energy balance (starvation and/or excessive exercise) is also detrimental for health and survival. It therefore becomes important to establish parameters of IMS (frequency, duration and ‘intensity’) that promote optimal brain function and disease resistance.

Thus far, we have considered the metabolic and cell-signalling-mediated adaptations of the brain to IMS, with a focus on the events occurring during the period of metabolic challenge (during fasting and exercise). However, events occurring in the brain during the recovery period (eating after fasting, resting after exercise and sleep) are also important to understand when considering IMS and neuroplasticity (FIG. 3). In this regard, knowledge of how muscle cells respond to exercise and recovery cycles provides a general framework for

understanding how IMS affects brain cells. The cellular stress that muscle cells experience during exercise activates several key pathways of the conserve-resources mode, including inhibition of mTOR and overall protein synthesis, upregulation of autophagy and upregulation of genes encoding antioxidant enzymes, sirtuins, protein chaperones and lipolytic enzymes[181]. The latter genes are induced by Ca^{2+}, ROS and an increase in the AMP:ATP ratio, which activate kinases (CaMKII and AMPK) and downstream transcription factors (nuclear regulatory factor 2 (NRF2; also known as NFE2L2), NRF1, peroxisome proliferator-activated receptors (PPARs) and forkhead box protein O1 (FOXO1)). PGC1α is also rapidly upregulated to facilitate the mitochondrial biogenesis that occurs during the subsequent recovery period after exercise; muscle cells grow not during the exercise period but rather during the recovery period. The sequential upregulation of autophagy and stress-resistance pathways during the exercise period and mitochondrial biogenesis and cell growth during the recovery period are both critical for the improvements in endurance and strength that result from intermittent exercise[181].

We suggest that a generally similar scenario occurs at the cellular and molecular levels in response to IMS in many neuronal networks in the brain (FIG. 3). Neurons respond to the G-to-K switch by downregulating mTOR and global protein synthesis while concomitantly upregulating cellular stress-resistance pathways and autophagy. Upstream triggers of the latter pathways include BHB, Ca^{2+} (CaMKII) and ROS, which activate transcription factors including CREB, NF-κB and PGC1α[182]. The latter pathways not only bolster cellular stress resistance but also set the stage for the structural and functional neuroplasticity that occur during the K-to-G recovery phase of IMS cycles. In this view, outgrowth of dendrites and axons, synaptogenesis and neurogenesis occur during the recovery phase, when the cells are in growth mode, with high levels of mTOR activity, protein synthesis and mitochondrial biogenesis. We envision that IMS involves alternating cycles of upregulation of neuronal autophagy and stress-response pathways when the switch is on and the expansion or adaptive remodelling of neuronal circuits when the switch is off (FIG. 3). This model does not preclude structural and functional adaptations (for example, dendritic spine formation or retraction, LTP and long-term depression) during periods of time when the switch is on. With regards to IMS and cognition, this hypothesis could be tested in experiments in which individual neurons are interrogated by time-lapse imaging and electrophysiological recordings during cycles of fasting and feeding. Experiments in which mTOR and PGC-1α are (genetically or pharmacologically) inhibited or upregulated during on and off phases of IMS cycles and synaptic plasticity, neurogenesis and cognition are evaluated would provide cause–effect data to support (or not) our working model.

Although IMS can enhance brain function and stress resistance, the question of what specific IMS regimen(s) is ideal for brain health throughout the life course remains unanswered. This could first be addressed in animal studies by systematically varying the duration of fasting and feeding periods (for example, ADF versus 16 hours daily TRF versus fasting 2 days per week) and evaluating behavioural, and the related electrophysiological and neurochemical, end points. Ideally, such experiments would be done in several strains of mice and/or rats and would include both males and females and ageing cohorts. To increase relevance to animals in the wild and human diet and lifestyle interventions, different exercise regimens could be incorporated into IF studies. Although an increasing number of studies have

demonstrated improvements in a range of peripheral health indicators when individuals who had previously eaten three or more meals every day change their eating pattern to an IF diet[182], data on the impact of IMS on the human brain are sparse. However, a recent study showed that a 2-year multidomain intervention (diet, exercise, cognitive training and vascular risk monitoring) results in improved scores on cognitive tests in elderly subjects compared with a nonintervention control group[183]. Randomized controlled trials of IF and exercise regimens with neurological end points (psychological test batteries, functional brain imaging and molecular interrogation of cerebrospinal fluid) at baseline and at designated time points during the IMS period will be of great value. On the basis of the evidence from the animal studies reviewed in this article, one might predict that IMS will improve mood and cognition, change resting-state and task-related neuronal network activity, increase levels of neurotrophic factors and reduce markers of inflammation in cerebrospinal fluid. Performance of such IMS trials in subject populations at risk of a neurological disorder (for example, subjects with metabolic syndrome), in subjects who have suffered an acute neurological insult and in patients in the early stages of an age-related neurodegenerative disorder may eventually lead to prescriptions for IMS instead of or in conjunction with drugs that target a specific pathway.

Conclusions and future directions

The evidence reviewed in this article leads to several general conclusions regarding IMS and neuroplasticity. First, cognition, sensory–motor function and physical performance can be enhanced by IMS protocols involving IF and/or vigorous exercise. Second, by providing an alternative energy source and activating signalling pathways involved in neuroplasticity and cellular stress resistance, the ketone BHB plays a particularly important role in neuronal adaptations to fasting and exercise. Third, neurons respond to the G-to-K switch by engaging a ‘cell-preservation mode’ and adopt a ‘cell-growth mode’ by activation of certain signalling pathways when the switch is off (food, rest and sleep). Fourth, fasting and exercise upregulate neurotrophic factor signalling, antioxidant and DNA repair enzymes, protein deacetylases and autophagy, which protects neurons against stress and sets the stage for mitochondrial biogenesis and cell growth and plasticity during recovery periods (FIG. 3). Fifth, lifestyles characterized by little or no IMS (three meals per day plus snacks and negligible exercise) result in suboptimal brain functionality and increase the risk of major neurodegenerative and psychiatric disorders. Sixth, many different IMS regimens are likely to improve brain health such that individuals may choose an approach that suits their particular daily and weekly schedules.

There are many gaps in our knowledge of the neurobiology of IMS and the application of such knowledge to the prevention and treatment of neurological disorders. Among the outstanding questions, we find the following particularly pressing. First, what adaptive responses of the nervous system to metabolic switching are mediated by and/or require ketones? This might be answered by studies in which the ketone-generating enzyme 3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) or neuronal monocarboxylate transporter 2 (MCT2; also known as SLC16A7) is knocked down or out in mice and then neurological responses to fasting and exercise are evaluated. Because of the criticality of ketones for survival during fasting, such experiments will require ‘titration’ of circulating

ketone levels by administration of exogenous ketones. Second, what are the contributions of intrinsic neuronal network signalling pathways and peripheral signals entering the brain from the circulation to IMS-induced neuroplasticity? Third, which pathways are common to the mechanisms of action of exercise, fasting and cognitive challenges, and which are unique to a specific metabolic challenge? Fourth, are there retrograde transneuronal signals from the peripheral nervous system to the CNS that mediate effects of IMS on CNS neuroplasticity and resistance to injury and disease? Fifth, are there roles for glial cells in adaptations of the CNS to IMS? Although IF and exercise can suppress microglia-mediated neuroinflammation, the underlying mechanisms remain to be established. The possible effects of IMS on astrocytes are also unexplored. Do IF and/or exercise stimulate neurotrophic factor production in astrocytes, and are ketones involved? Does IMS affect axonal myelination? Sixth, are there roles for cerebrovascular remodelling in the beneficial effects of IMS on cognition and stress resistance, and what are the underlying mechanisms? Seventh, does IF improve cognition in humans, and which cognitive domains are affected? Eigth, will there be clinical applications of IMS ‘prescriptions’ for a range of neurological disorders? Several randomized controlled trials of IF in subjects with or at high risk of a neurological disorder are in progress, and results will be forthcoming.

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Glossary

β-Hydroxybutyrate(BHB)
A ketone, generated from fatty acids during fasting and extended exercise, that functions as a cellular energy source and as a signalling molecule that induces the expression of brain-derived neurotrophic factor.

Intermittent metabolic switching (IMS)
Repeating cycles of a metabolic challenge (fasting and/or exercise) sufficient to deplete liver glycogen stores and elevate circulating ketone levels, followed by a recovery period (eating, resting and sleeping).

Brain-derived neurotrophic factor (BDNF)
A protein produced and released from neurons in response to synaptic activity, exercise and fasting that acts to enhance synaptic plasticity and cellular stress resistance.

Mitochondrial biogenesis
The proliferation of mitochondria in neurons in response to metabolic challenges and neurotrophic factors to produce new mitochondria that promote synaptic plasticity and cellular stress resistance.

Deacetylase
An enzyme that removes an acetyl group from lysine residues of substrate proteins; the sirtuins SIRT1 and SIRT3 are deacetylases that play particularly important roles in adaptive responses of neurons to metabolic challenges.

Mechanistic target of rapamycin
(mTOR; also known as serine/threonine-protein kinase mTOR (MTOR) and mammalian target of rapamycin). A kinase that plays a pivotal role in stimulating cellular protein synthesis and suppressing autophagy when nutrients (glucose and amino acids) are plentiful.

Autophagy
A complex process by which cells recognize damaged dysfunctional proteins and organelles, engulf them in a membrane and target them for enzymatic degradation in lysosomes to generate recyclable undamaged components (for example, amino acids and lipids).

Ketogenesis
The process by which spillover of acetyl CoA results from β-oxidation of fatty acids in the liver during fasting and extended exercise.

Myokines
Proteins and peptides released from muscle cells during exercise that can enter the brain and affect neuroplasticity; examples include interleukin-6, cathepsin B and irisin.

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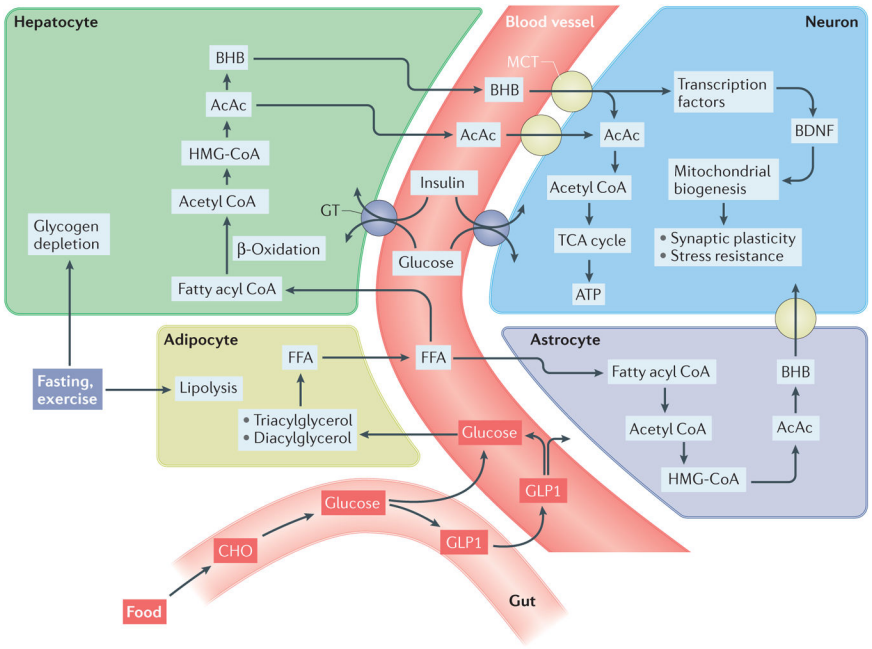

Figure 1. Biochemical pathways involved in the metabolic switch

During fasting and sustained exercise, liver glycogen stores are depleted and lipolysis of triacylglycerols and diacylglycerols in adipocytes generates free fatty acids (FFAs), which are then released into the blood. The FFAs are transported into hepatocytes, where they are metabolized via β-oxidation to acetyl CoA, which is then used to generate the ketones acetone, acetoacetate (AcAc) and β-hydroxybutyrate (BHB). BHB and AcAc are transported from the blood into the brain and then into neurons via monocarboxylic acid transporters (MCTs) in the membranes of vascular endothelial cells and neurons. Within neurons, BHB and AcAc are metabolized to acetyl CoA, which then enters the tricarboxylic acid (TCA) cycle in mitochondria, resulting in the production of ATP and the reducing agents that transfer electrons to the electron transport chain. BHB can also upregulate the expression of brain-derived neurotrophic factor (BDNF) and may thereby promote mitochondrial biogenesis, synaptic plasticity and cellular stress resistance. In addition to blood-borne ketones, astrocytes are capable of ketogenesis, which may provide an important local source of BHB for neurons. Intermittent metabolic switching also increases insulin sensitivity, thereby enhancing uptake and utilization of glucose by neurons. Upon refeeding, ingested carbohydrates (CHO) and glucose stimulate release into the blood of the incretin hormone glucagon-like peptide 1 (GLP1) from enteroendocrine cells in the gut. GLP1 enhances clearance of glucose from the blood by stimulating insulin release from the pancreas and increases the insulin sensitivity of cells. GLP1 crosses the blood–brain barrier and can act directly on neurons to promote synaptic plasticity, enhance cognition and bolster cellular stress resistance. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; GT, glucose transporter.

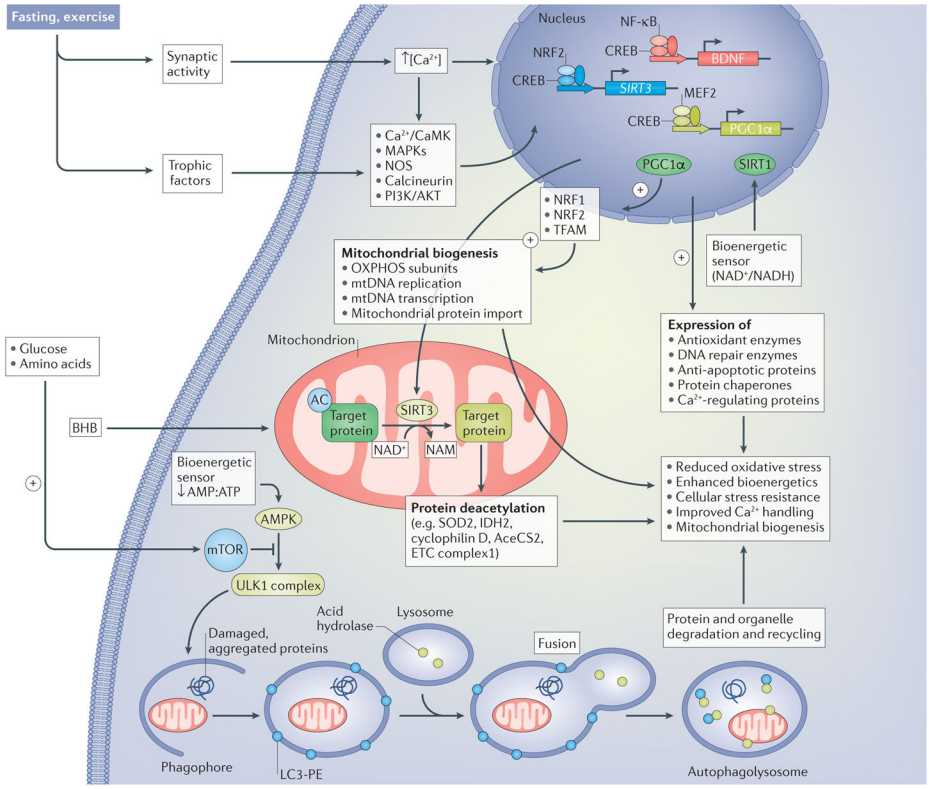

Figure 2. Signalling pathways by which neurons respond to the metabolic switch during fasting and exercise

Increased excitatory synaptic activity triggers Ca^{2+} influx through plasma membrane channels, resulting in the activation of multiple kinases, including calcium/calmodulin-dependent kinases (Ca^{2+}/CaMK) and mitogen-activated protein kinases (MAPKs), nitric oxide synthase (NOS) and the protein phosphatase calcineurin. Neurotrophic factor signalling pathways are also engaged in response to fasting and exercise, resulting in the activation of signalling pathways involving phosphatidylinositol 3-kinase (PI3K), RACα serine/threonine-protein kinase (AKT) and MAPKs. These activity-dependent and neurotrophic-factor-dependent signalling pathways converge on transcription factors, including cAMP-responsive element-binding protein (CREB), nuclear regulatory factor 2 (NRF2; also known as NFE2L2), nuclear factor-κB (NF-κB) and myocyte-specific enhancer factor 2 (MEF2), which induce the expression of many different genes that encode proteins involved in cellular stress adaptation. Three genes that may be particularly important in the enhancement of neuroplasticity and stress resistance in response to intermittent metabolic switching are those encoding brain-derived neurotrophic factor (BDNF), NAD-dependent protein deacetylase sirtuin 3 (SIRT3) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α). SIRT3 localizes to the mitochondria, where it deacetylates proteins involved in antioxidant defence (superoxide dismutase [Mn], mitochondrial (SOD2)), energy production (isocitrate dehydrogenase [NADP], mitochondrial (IDH2); acetyl CoA synthase 2 (AceCS2; also known as ACSS1); and electron transport chain (ETC) proteins) and protection against apoptosis (cyclophilin D). PGC1 α is a key transcriptional regulator of mitochondrial biogenesis that acts, in part, by upregulating NRF1 and

mitochondrial transcription factor A (TFAM), which, in turn, upregulate oxidative phosphorylation, mitochondrial DNA (mtDNA) replication and transcription and mitochondrial protein import. CREB, NRF2 and NF-κB induce the expression of antioxidant enzymes, DNA repair enzymes, anti-apoptotic proteins and protein chaperones and Ca^{2+}-handling proteins. The ketone β-hydroxybutyrate (BHB), which is elevated during fasting and extended exercise, provides an energy substrate for neurons and induces the expression of BDNF. The reduction in availability of glucose and amino acids during fasting and exercise results in a reduction in the AMP:ATP ratio, which activates AMP kinase (AMPK) and, in turn, stimulates autophagy. The reduction in glucose and amino acid availability also reduces activation of mammalian target of rapamycin (mTOR) and further enhances the AMPK-driven autophagy pathway. AMPK activates the serine/threonine-protein kinase ULK1 (ULK1) complex, which stimulates engulfment of damaged proteins and organelles in autophagosomes, which, in turn, fuse with lysosomes. Collectively, activation of these different pathways in response to the metabolic switch bolsters neuronal bioenergetics, improves Ca^{2+} handling and protects against oxidative, excitotoxic and proteotoxic stress. AC, acetyl group; LC3-PE, light chain 3– phosphatidylethanolamine; NAM, nicotinamide adenine mononucleotide; OXPHOS, ETC complexes involved in oxidative phosphorylation.

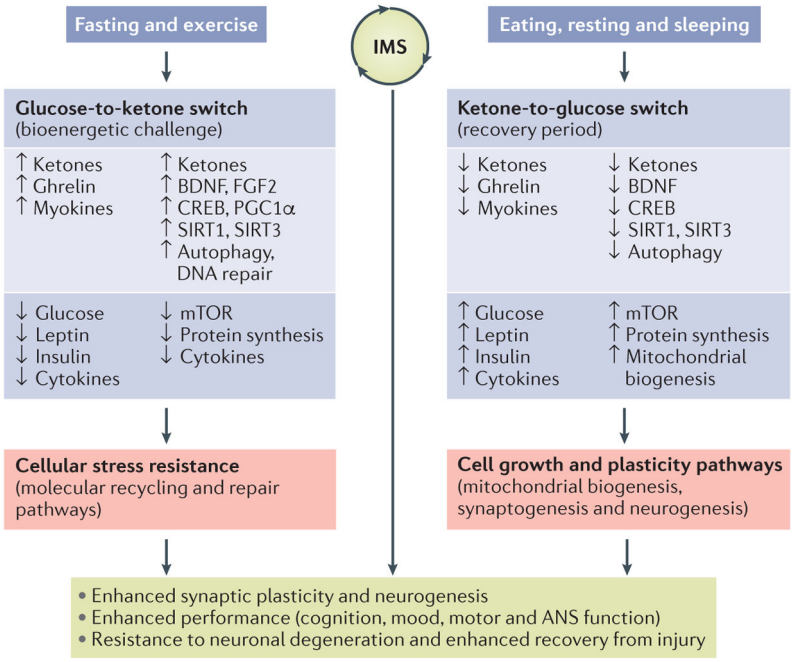

Figure 3. Model for how intermittent metabolic switching may optimize brain performance and increase resistance to injury and disease

Intermittent metabolic switching (IMS) involves repeating time periods of a bioenergetic challenge (fasting and/or exercise) when the metabolic switch is on (that is, liver glycogen stores are depleted and ketones are produced) and recovery periods (eating, resting and sleeping) when the metabolic switch is off. When the metabolic switch is on, levels of circulating ketones, ghrelin and myokines are elevated, whereas levels of glucose, leptin, insulin and pro-inflammatory cytokines are maintained at low levels. Adaptive responses of neurons to fasting and exercise include utilization of ketones as an energy substrate; increased expression of brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF2); activation of the transcription factors cAMP-responsive element-binding protein (CREB) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α), which induce the expression of genes involved in synaptic plasticity, neurogenesis and mitochondrial biogenesis; and upregulation of autophagy and DNA repair pathways. During the bioenergetic challenge, activity of the mammalian target of rapamycin (mTOR; also known as serine/threonine-protein kinase mTOR (MTOR) and mechanistic target of rapamycin) pathway and global protein synthesis are reduced in neurons, and levels of pro-inflammatory cytokines in the brain are reduced. Collectively, the pathways activated when the metabolic switch is on enhance neuronal stress resistance and bolster repair and recycling of damaged molecules. When the metabolic switch is off, circulating levels of glucose, leptin, insulin and pro-inflammatory cytokines increase, whereas levels of ketones, ghrelin and myokines decrease. In brain cells, the mTOR pathway is active, protein synthesis increases and mitochondrial biogenesis occurs during the recovery period. The activation state of neurotrophic signalling and adaptive cellular stress-response pathways may decrease when the metabolic switch is off. Cycles of IMS may optimize brain health by promoting synaptic plasticity and neurogenesis, improving cognition, mood, motor performance and autonomic nervous system (ANS) function and bolstering resistance of

neurons to injury and neurodegenerative disease. SIRT, NAD-dependent protein deacetylase sirtuin.