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Mini review

Positive effects of intermittent fasting in ischemic stroke

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ABSTRACT

Intermittent fasting (IF) is a dietary protocol where energy restriction is induced by alternate periods of *ad libitum* feeding and fasting. Prophylactic intermittent fasting has been shown to extend lifespan and attenuate the progress and severity of age-related diseases such as cardiovascular (e.g. stroke and myocardial infarction), neurodegenerative (e.g. Alzheimer's disease and Parkinson's disease) and cancerous diseases in animal models. Stroke is the second leading cause of death, and lifestyle risk factors such as obesity and physical inactivity have been associated with elevated risks of stroke in humans. Recent studies have shown that prophylactic IF may mitigate tissue damage and neurological deficit following ischemic stroke by a mechanism(s) involving suppression of excitotoxicity, oxidative stress, inflammation and cell death pathways in animal stroke models. This review summarizes data supporting the potential hormesis mechanisms of prophylactic IF in animal models, and with a focus on findings from animal studies of prophylactic IF in stroke in our laboratory.

1. Overview of neuroprotective mechanisms in intermittent fasting (IF)

The protective effects of prophylactic intermittent fasting (IF) have been shown to prevent and attenuate cellular dysfunction and degeneration in the brain by preconditioning neurons and glial cells with energy restriction in rodent diseased models (Mattson and Wan, 2005; Mattson et al., 2016). Prophylactic IF appears to act as a mild metabolic stressor that effectively upregulates the expression of several key neuroprotective proteins observed in the brain in rodent diseased models. These neuroprotective proteins include neurotrophic factors (e.g. brain-derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF)), stress response proteins (e.g. heat shock protein 70 (Hsp70) and glucose regulated protein 78 (GRP78)), regulatory proteins (e.g. peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)), antioxidant enzymes (e.g. heme oxygenase-1 (HO-1)) and uncoupling proteins (e.g. UCP2 and UCP4), in addition to down regulation of mammalian target of rapamycin (mTOR) activity (Akerfelt et al., 2010; Arumugam et al., 2010; Chu et al., 2009; Liu et al., 2006; Mattson and Wan, 2005; Tajes et al., 2010; Vasconcelos et al., 2014) However, the precise mechanism(s) by which prophylactic IF induces the expression of these neuroprotective proteins in animal brains remains to be fully established. Nevertheless, it is known that energy depletion induced by IF in cells will activate energy sensor proteins such as adenosine monophosphate (AMP)-activated protein kinase (AMPK), and silent information regulator-1 (SIRT1) through their respective phosphorylation and deacetylation reactions in response to increases in the AMP/ATP, and nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydrogenated (NAD^+/NADH) ratio, respectively, in the brains of diseased rodent models (Braidy et al., 2014; Burkewitz et al., 2014; Cantó and Auwerx, 2011; Chen et al., 2008; Gräff et al., 2013; Mouchiroud et al., n.d.; Tajes et al., 2010; Zhang et al., 2011). Hence, it is suggested that the protective effects of prophylactic IF are primarily mediated by the activation of AMPK and SIRT1, and their downstream upregulation of several key neuroprotective protein targets that synergistically interact to increase cellular resistance against a number of molecular and cellular pathological processes that occur in brain injury; especially, excitotoxicity, oxidative stress and inflammation during an ischemic stroke, in addition to regulating neurogenesis and angiogenesis in rodent stroke models (Fig. 1).

2. Mechanisms of ischemic stroke

During an ischemic stroke, a complicated cascade of events will be activated spatially and temporally to induce damage to cerebrovascular tissue. The brain is an organ that requires an enormous demand for both oxygen and glucose in order to meet its energy requirements in the form of adenosine triphosphate (ATP). As such, oxidative phosphorylation is highly depended upon in order to meet this demand. However, cerebral ischemia restricts the access of both oxygen and glucose substrates to the brain causing insufficient ATP synthesis, despite continued consumption. As a result, total ATP stores decrease and the brain experiences energy failure. Moreover, since energy is needed to maintain ionic gradient homeostasis in neuronal and glial cells, energy failure is normally followed by the concomitant loss of membrane potential and

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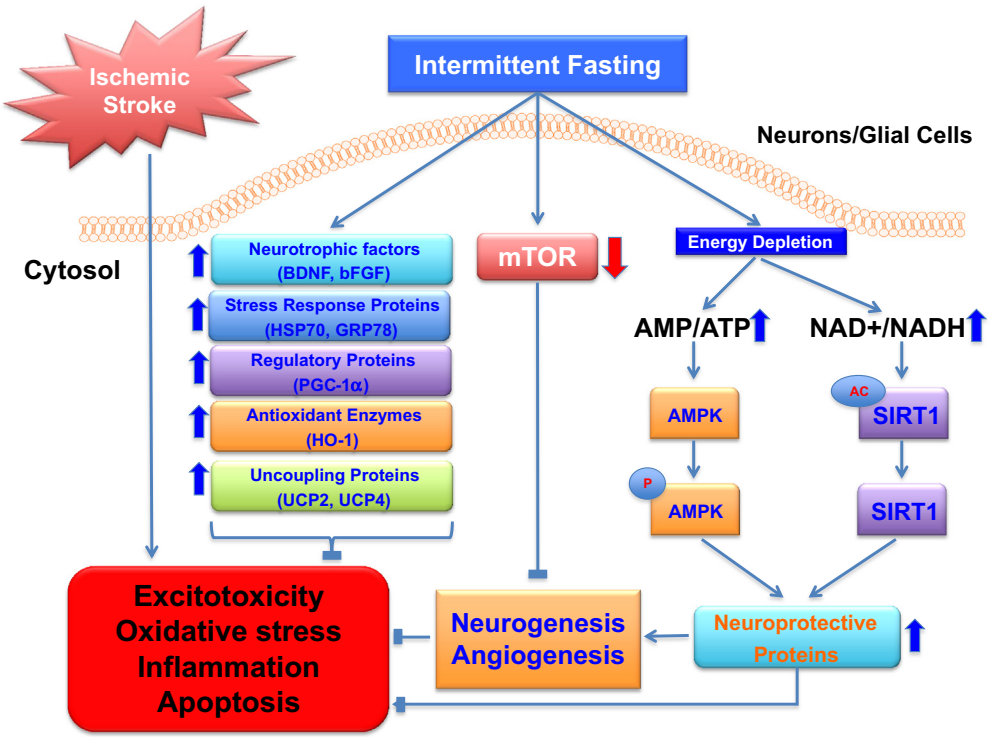

Fig. 1. Intermittent fasting (IF) may serve as a mild metabolic stressor to neurons or glial cells, leading to upregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF); stress response proteins including protein chaperones such as heat shock protein 70 (Hsp70) and glucose regulated protein 78 (GRP78); regulatory proteins, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α); antioxidant enzymes, such as heme oxygenase-1 (HO-1); and uncoupling proteins, such as UCP2 and UCP4. Concurrently, IF may be able to induce the downregulation of mammalian target of rapamycin (mTOR). In addition, high AMP/ATP and NAD^+/NADH ratio due to energy depletion may occur during IF and may result in the activation of energy sensors adenosine monophosphate (AMP)-activated protein kinase (AMPK), and silent information regulator-1 (SIRT1) through phosphorylation and deacetylation reactions, respectively. In summary, the following cellular pathways have the potential effect of increasing cellular resistance against pathological outcomes of ischemic stroke such as excitotoxicity, oxidative stress and inflammation; in addition to favoring neurogenesis and angiogenesis, to potentially help attenuate the pathological damage incurred during an ischemic stroke.

depolarization subsequently ensues. Damage from biological waste products such as lactate also occurs via acidosis (Dirnagl et al., 1999; Philp et al., 2005; Pulsinelli, 1992). Cells in the infarct core region undergo greater loss in membrane potential and depolarization, yet are unable to repolarize again in the ischemic brain. Conversely, cells in the penumbra region still demonstrate an ability to repolarize, but such process comes with a huge sacrifice of even greater energy consumption, creating a deleterious cycle. As such, cells in the penumbra region exhibit repeated depolarization, termed peri-infarct depolarization. As the number of depolarization increases spatially over time, the infarct core region increases worsening neurological function (Hartings et al., 2003; Hossmann, 2012; Umegaki et al., 2005).

The concomitant energy failure demonstrated following ischemia, as well as loss of ionic homeostasis, leads to the activation of glutamate receptors, which is a major player in mediating ischemic cell death in the brain. Glutamate, an excitotoxic neurotransmitter binds to its receptors such as ionotropic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), leading to an intracellular influx of calcium ions in neurons (Meldrum, 2000; Weber, 2012). Under normal circumstances, energy-dependent presynaptic reuptake of these excitotoxic neurotransmitters can be performed. However, following a depletion of ATP during energy failure, such process is inhibited and glutamate remains in the extracellular space, leading to continuous activation of glutamate receptors on neurons that contribute to intracellular Ca^{2+} accumulation. Intracellular Ca^{2+} overload is able to activate phospholipases and proteases, leading to the degradation of membranes and proteins, respectively, as well as nucleases in neurons (Berliocchi et al., 2005; Cheng et al., 2012; Dong et al., 2009; Khatri and Man, 2013; Santos et al., 1996). Furthermore, activation of glutamate receptors also causes a massive influx of Na^+ and efflux of K^+ ions across the plasma membrane in neurons, disrupting the ionic gradient and contributing to anoxic depolarization, previously described. Cellular influx of Na^+ ions is accompanied with an influx of water into neurons and glial cells, causing it to swell and exhibit cytotoxic tissue edema in the brain. The resulting cytoplasmic edema induces adverse effects on cerebrovascular tissues, leading to symptoms like intracranial pressure stress, compression of vasculature, as well as brain herniation (Bragin et al., 2011; Lai et al., 2014; Liang et al., 2007). The resulting high intracellular concentration of Ca^{2+} and Na^+ ions, and high intracellular adenosine diphosphate (ADP): ATP ratio in neurons and glial cells following ischemia leads to mitochondria dysfunction, endoplasmic reticulum (ER) stress and production of reactive oxygen species (ROS). Due to the unstable nature of ROS, macromolecules in neurons and glial cells such as DNA, proteins, lipids and carbohydrates are oxidized, and consequently structurally modified and damaged, triggering a myriad of cell death processes such as necrosis, apoptosis, and autophagy in the brains of rodent ischemic stroke models (Chaudhari et al., 2014; Ricci and Zong, 2006; Zeeshan et al., 2016).

Inflammatory mediators, such as pro-inflammatory cytokines and chemokines, are quickly produced by neuronal, glial and endothelial cells following an ischemic event, due to the presence of high levels of intracellular Ca^{2+} and ROS, in addition to a low oxygen environment in the brain (hypoxia). These inflammatory mediators are able to induce the expression of a myriad of adhesion molecules such as selectins (e.g. P-selectins) or intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, platelets and leukocytes in the brain following an ischemic stroke (Ala et al., 2003; Ceulemans et al., 2010; Ramesh et al., 2013; Séïté et al., 2014). As a result, migration of immune cells such as neutrophils and macrophages will follow, which mediate secondary ischemic reperfusion injury in the brain. Many studies conducted recently have pointed out the emerging roles of inflammasomes in mediating inflammatory responses in the brain in rodent models of ischemic stroke