Commentary

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Much ado about eating: Intermittent fasting and post-stroke neuroprotection

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Abstract

A proper diet is important for health and longevity. Controlling the amount of food consumed is immensely beneficial as it promotes multiple cellular and molecular protective mechanisms and simultaneously prevents toxic mechanisms. Intermittent fasting (IF) is a flexible and easy-to-adopt dietary modification that helps to mitigate metabolic disorders like diabetes and hypertension, and thus the devastating age-related diseases like heart attack, stroke and dementia. The benefits of IF seem to be mediated by altered epigenetic and transcriptional programming leading to reduced oxidative stress, inflammation, mitochondrial damage and cell death.

Keywords

Caloric restriction, cerebral ischemia, preconditioning, inflammation, cell death

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In humans, an active lifestyle combined with healthy eating style retards metabolic disorders and prevents cardiovascular and neurodegenerative diseases. Dietary interventions such as caloric restriction (CR) and intermittent fasting (IF) lead to systemic changes via molecular and cellular adaptations and improve glucose and lipid balance as well as control blood pressure in both humans and animals. These changes delay the onset and development of diseases in comorbid and aged individuals. Indeed, experimental studies in animal models revealed that both IF and CR confer protection against ischemic stroke, Alzheimer's Diseases (AD) and other age-related metabolic, cardiovascular and brain diseases.[1,2] CR was shown to release adioponectin (aPM1), which controls glucose homeostasis and the post-ischemic protection by CR was lost in aPM1 knockouts.[2] Particularly, IF is a flexible and easily adoptable lifestyle change where a person can still eat all the calories/day, but only during a period of 8 to 12 hours. IF is thought to be beneficial even if followed on only some days of the week. Of all CNS disorders, preconditioning is more appropriate for stroke as high-risk subjects with comorbid conditions are identifiable. Of the various approaches, diet control is a safe and easily adoptable preconditioning paradigm in these cohorts.

The benefits of IF are multi-pronged. Post-stroke brain damage is mediated by several pathologic changes including oxidative stress, inflammation, mitochondrial damage and misfiring of gene expression (Figure 1). IF switches the energy use from glucose to ketone bodies, and thus increases NAD^+ levels that induces SIRT1. This leads to the activation of SIRT1 downstream transcription factors PGC-1α and NRF2 and further downstream Mn-SOD, catalase and the glutathione and thioredoxin antioxidant systems to efficiently detoxify ROS.[3] Higher levels of NAD^+ also uncouples mitochondria, and thus reduces superoxide production and oxidative DNA damage. Furthermore, SIRT1 inhibits FoxO1 and NF-kB leading to curtailed inflammatory gene expression. NAD^+ also inactivates mTOR pathway leading to reduced

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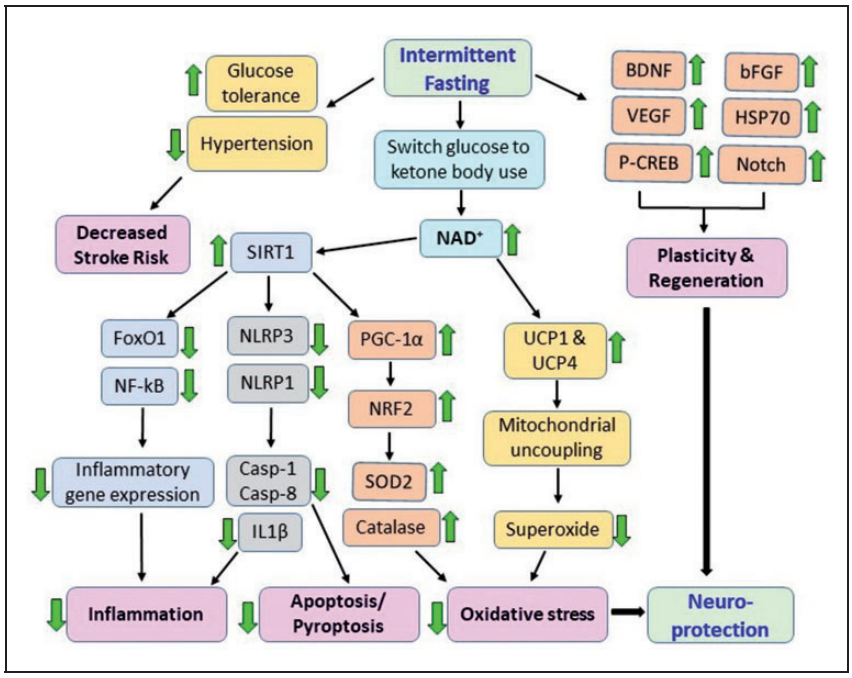

Figure 1. Intermittent fasting (IF) influences the body by multiple mechanisms. IF increases glucose tolerance and controls blood pressure. This leads to better prognosis as diabetes and hypertension are major comorbid conditions for stroke. IF induces several genes that promote plasticity, regeneration and neuroprotection. IF also promotes the pathways that curtail inflammation, oxidative stress and apoptosis leading to neuroprotection after stroke.

expression of pro-inflammatory cytokines and thus decreased inflammation in case of an injury.[4] IF is also known to activate mitochondrial uncoupling proteins (UCP2 and UCP4) and mitochondrial biogenesis leading to increased mitochondrial respiratory rate.[4] Post-ischemic induction of cerebral inflammasomes NLRP1 and NLRP3 and microglial activation, which significantly contribute to inflammation were also shown to be curtailed in rodents subjected to IF.[5] NLRP1 and NLRP3 also activate the pro-death caspases and hence their prevention by IF leads to decreased apoptotic and pyroptotic cell death.

IF was shown to extensively alter the post-ischemic gene expression in multiple organs.[6] In essence, IF induces several classes of beneficial genes including those that modulate metabolism, signal transduction, cell survival and growth factors and concomitantly suppresses many pro-inflammatory, pro-apoptotic and pro-oxidant genes. IF is also known to increase plasticity and thus long-term functional outcomes under health conditions as well as after a CNS insult. For example, IF was shown to promote both memory acquisition and retention in healthy rodents.[7] These benefits might be due to the induction of trophic and growth factors like BDNF, bFGF and VEGF and protein chaperones like HSP70.[8] IF was also shown to induce p-CREB that activates Notch signaling leading to neurogenesis.[9] In addition, VEGF promotes angiogenesis that also improves the plasticity.

Aging is a major precipitator of stroke as well as post-stroke functional deficits. While the benefits of IF in promoting ischemic tolerance in aged individuals is not yet evaluated systematically, studies showed that IF promotes motor and cognitive functions in middle-aged rats[10] as well as older humans.[11] Importantly, IF was also shown to significantly alter the expression of genes that control circadian clock and autophagy in humans that are known to retard age-induced changes in the body.[12] IF seems to work synergistically with other neuroprotective/preconditioning paradigms. When humans were subjected to IF + exercise, there was a decrease in the expression of several pro-inflammatory molecules.[13] When IF was combined with the extracts of *Withania somnifera* and *Tinospora cordifolia* (herbal supplements), there was reduced inflammation and decreased anxiety like behavior in rodents.[10]

To conclude, IF is a beneficial dietary adaptation that can precondition the body to promote tolerance to stroke by decreasing oxidative stress, inflammation, and promoting the expression of genes that are essential for plasticity and regeneration. However, the benefits of IF in post-stroke recovery need to be studied more rigorously in aged subjects of both sexes as well

as comorbid subjects. Future studies also need to show if combining IF with other practices like exercise can further increase the ischemic tolerance in comorbid subjects.

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Authors' contributions

Both the authors conceptualized and wrote this commentary together.

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