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EFFECTS OF INTERMITTENT FASTING ON COGNITION AND NEURODEGENERATION

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ABSTRACT:

Intermittent fasting (IF) can facilitate neurodegenerative, neuroadaptive and neuroprotective processes leading to profound effects on cognition and dementias. The impact that IF has on the central nervous system is still not fully known. Several factors come into likely effect including changes in energy metabolism, oxidative damage, insulin sensitivity, inflammation, and functional changes related to various neurotransmitters and hormones. During IF ketones are produced in large quantities and the brain consumes these for energy. The presence of ketone bodies increases the expression of the genes for brain derived neurotrophic factor which has a powerful effect on dementia and cognition. Brain derived neurotrophic factor (BDNF) in the hippocampus, the striatum, and cerebral cortex affects learning capabilities and memory. This process is enhanced by IF. IF also has multiple effects on the endocrine wellbeing, including control of hypertension, metabolic syndrome, insulin resistance and dyslipidemia. In ancient times, fasting was a common practice but with recent cellular studies the beneficial effects on the brain of IF are being truly proven. In a world of costly health care with an increase in neurological disorders, IF could be an effective therapy that is multi targeted, self-controlled and cost free .Further research is required to question the effect of IF in the long-term and whether pharmaceuticals can come up with safer medication options that imitate the effects of IF without a drastic change in the eating patterns.

KEYWORDS:
Intermittent Fasting(IF), Cognition, Dementia, Brain derived neurotrophic factor (BDNF)

INTRODUCTION:

The current living norms are such that most people have excessive food accessibility with relatively decreased physical activity. Intermittent fasting (IF) implies an eating plan that switches between eating and fasting on a regular pattern. It is not a diet in the conventional sense but a very popular fitness ritual. Its success more so relies on vast periods of complete absence of diet and not what one intake. There are many protocols in practice for intermittent fasting including lean gains protocol and eat- stop-eat protocol. In lean gains protocol subjects are allowed to eat eight hours followed by sixteen hours fasting while eat-stop-eat protocol allows fasting for twenty fours once a week. Another protocol popular as 5;2 diet allows subject to consume only 500 calories daily for two days and normal eating for five days.[1] Muslims fast from dawn until dusk during one month in the year -Ramadan. While Christians, Jews, Buddhists, and Hindus have different traditions to their fating ritual. There is ample evidence from history that fasting was observed anciently by the greats like Hippocrates who believed in a pure water only fast as a method of healing or Plato who fasted for better physical and mental efficiency. Interestingly there is recent research that claims intermittent fasting may affect cognition and dementias like Alzheimer's disease.

COGNITION AND DEMENTIA: DEFINITION AND BURDEN

Dementia is one of the most common neurological diseases especially among elderly. Its presenting features include functional disability with memory changes and cognitive deficits. The American Psychiatric Association' fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) states Dementia as a major neurocognitive disorder (NCD) and mild cognitive impairment (MCI) as a mild NCD. The DSM-5 details cognitive domains which may be affected in both mild and major NCD including executive function, learning and memory, language, and perceptual motor functions. Current global prevalence of dementia is around 50 Million with more than half living in low income and middle-income countries. This number is supposed to reach up to 66

million by 2030 and up to 115 million by 2050.2 Alzheimer disease (AD) is the most common form of dementia and may contribute to 70-80 % of cases.2 It is a major cause of disability among elderly population. Burden of care of dementia patients lies with family and health care system. Dementia care expenditure may be leading financial burden for many health care systems in coming years. Lack of awareness leads to increase care giver burden and financial resources.[2]

CELLULAR EFFECTS OF INTERMITTENT FASTING:

There are several adaptive cellular responses due to IF. After meals glucose is used for energy usually and fat is stored as triglycerides in adipose tissue. During fasting triglycerides are broken down to fatty acids and glycerol and later converted to ketones by the liver. Oxidation of fatty acids leads to ketone bodies formation. In low glucose states, ketones become major energy source for brain. Ketones levels rise after 12 hours of fasting and remain elevated for 24-28 hours.[3 4] Ketone bodies are important signaling molecules with effects on cells and organ functions.[5] They regulate the expression of many proteins and molecules including fibroblast growth factor 21,nicotinamide adenine dinucleotide (NAD) and peroxisome proliferator activated receptor etc. with profound effects on systemic metabolism.[6] Ketone bodies also stimulate expression of the gene for brain derived neurotrophic factor.[7] Brain derived neurotrophic factor(BDNF) affects the learning and memory. IF has proven to stimulate BDNF in the various parts of brain. [8] A published article by a leading expert suggested caloric restriction leads to decreased production of oxygen free radicals. [9] Moreover IF enhances GABAergic inhibitory neurotransmission which can prevent excitotoxicity and seizures seen in around 10 percent patients with dementia.[10] Dietary changes may lead to changes in insulin sensitivity. [11]

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) IN FASTING:

It has been shown in research studies that intermittent fasting can increase BDNF expression in temporal lobes especially hippocampus. BDNF is a neurotrophin with multidimensional effects including plasticity and survival. It may affect neurogenesis stimulate neuron survival. Neurodegenerative disease for example Alzheimer's disease and Parkinsons Disease demonstrate decreased BDNF levels. In healthy volunteers, mean plasma BDNF levels were found to be approximately 92.5 pg./ml (8.0–927.0 pg./ml).[12] A recent study measured CSF concentration of BDNF, Aβ42 and total tau in patients with Alzheimer's disease and mild cognitive impairment and compared to cognitively normal subjects. Study showed BDNF levels were lower in patients with AD as compared to cognitively normal controls.[13]

INTERMITTENT FASTING AND NEURODEGENERATION:

Neurogenesis in adult hippocampus and its connections to prefrontal cortex are linked to learning and memory.[14] Mild stressors like exercise, enriched environment, and restricted daily intake were shown to increase new neuron formation corroborating the association between cognition and neuroplasticity. Underlying mechanisms contributing toward effects of fasting may include reduction in oxidative stress, neurotrophic signal enhancement, and improved bioenergetics. Reduced dietary intake and lack of available energy leads to a perceived cellular stress by neurons which in turn result in increased production of stress resistant response proteins.

Several mechanisms are responsible for synthesis of neurotropic factors especially brain derived neurotropic factor and anti-oxidative enzymes. These include peroxisome proliferator-activated receptors (PPARs), insulin-like fork head box O (FOXO) signaling factors and sirtuins (SIRTs). 26 Data from animal studies suggest anti amyloidogenic activity in rodent brains is maintained by increased generation of active A disintegrin and metalloproteinase 10 (ADAM10) proteins secondary to higher levels of SIRTI1. [15]

This increased level of active ADAM10 not only reduces Aβ but also can lead to reduction in Tau pathology and increased hippocampal neurogenesis. Alternate day fasting and daily caloric restriction reverses the adverse effects of obesity, diabetes and neuro inflammation on spatial learning and memory. The underlying mechanism in intermittent fasting is metabolic switching in which metabolism is switched from glucose to ketones. This mode of metabolism is main driver of health benefits observed in some clinical and pre-clinical studies.

ANIMAL STUDIES:

Intermittent fasting may enhance many cognitive domains including working memory, special memory, and associative memory. [16] Studies have demonstrated that short-term and medium-term intermittent fasting could have a neuroprotective effect by decreasing amyloid-β (Aβ) peptide aggregates and microglia activation. Studies have shown that , rats and mice maintained on an intermittent fasting routine exhibit less neuronal dysfunction and degeneration. [17] nother study looking at a rat model of menopause and Alzheimer's disease demonstrated that intermittent fasting may prevent some of the metabolic pathologies associated with

menopause and protect against age-related memory decline.[18]

HUMAN STUDIES AND META ANALYSIS:

A small study of fifty healthy subjects divided into three groups (controls; 30% caloric restriction and 20% increase in fat intake) for three months demonstrated a significant increase in verbal memory scores after caloric restriction. These scores correlated with high levels of CRP and decreased fasting plasma insulin levels. [19] Effect of intentional and substantial weight loss on cognitive function has been a topic of many research studies with assessment of cognitive function using validated tools before and after weight loss. A meta-analysis of these studies showed heterogenous outcome with modest and significant effect of weight loss on cognitive function. A significant association between weight loss and improvement in attention span and executive function was also reported. [20] A recent study from Canada showed that 2 years of caloric restriction in non-obese healthy adults led to a significant improvement in in working memory.[21] Epidemiological data suggests that excessive energy intake in midlife increases the risks of stroke and neurodegenerative diseases.[22] No clear consensus exists to prove a beneficial effect of fasting in the adolescent age. Some studies have also shown no impact or negative impact on school performance and cognition after short-term fasting. [23] Also at school going age a lot of confounders like socioeconomic status, psychopathological conditions, parents' education, and attitudes towards school would be difficult to take into perspective. IF improves insulin sensitivity, and thus prevents obesity. Six short term studies involving obese or overweight adults have shown that IF is as effective for weight loss as standard diets.[24]

FUTURE RESEARCH:

In a world of costly health care with increasing neurological disorders, IF could be an effective beneficial therapy that is multi targeted, self-controlled and cost free. Detailed, unified research studies are needed to investigate the possible implications of IF in the long-term. Also, the possible implications of IF for people who are within the normal body mass index Further research is needed at the pharmaceutical level for safer medication options that imitate the effects of IF without a drastic change in the eating patterns as long-term dietary and fluid restriction may have led to poor performance and non-sustained attention. An important research question would be to see the temporal effects on cognition as this may not be seen immediately and may have a more lasting impact. Physicians should provide adequate information and support to patients opting for IF as its implications may have considerable adverse effects such as irritability and reduced concentration especially in the beginning despite of evidence for health benefits.

REFERENCES:

1. Ganesan K, Habboush Y, Sultan S. Intermittent fasting: the choice for a healthier lifestyle. Cureus 2018;10:e294
2. Wortmann M. Dementia: a global health priority-highlights from an ADI and World Health Organization report. Alzheimer's research & therapy. 2012 Oct 1;4(5):40.
3. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell metabolism. 2014 Feb 4;19(2):181-92.
4. Browning JD, Baxter J, Satapati S, Burgess SC. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. Journal of lipid research. 2012 Mar 1;53(3):577-86.
5. Newman JC, Verdin E. β-Hydroxybutyrate: a signaling metabolite. Annual review of nutrition. 2017 Aug 21;37:51-76.
6. Gälman C, Lundåsen T, Kharitonenkov A, Bina HA, Eriksson M, Hafström I, Dahlin M, Åmark P, Angelin B, Rudling M. The circulating metabolic regulator FGF21 is induced b prolonged fasting and PPARα activation in man. Cell metabolism. 2008 Aug 6;8(2):169-74.
7. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity, and brain health. Nature Reviews Neuroscience. 2018 Feb;19(2):63.
8. Vasconcelos AR, Yshii LM, Viel TA, Buck HS, Mattson MP, Scavone C, Kawamoto EM. Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. Journal of neuroinflammation. 2014 Dec 1;11(1):85.
9. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. New England Journal of Medicine. 2019 Dec 26;381(26):2541-51.
10. Liu Y, Cheng A, Li YJ, Yang Y, Kishimoto Y, Zhang S, Wang Y, Wan R, Raefsky SM, Lu D, Saito T. SIRT3 mediates hippocampal synaptic adaptations to intermittent fasting and ameliorates deficits in APP mutant mice. Nature communications. 2019 Apr 23;10(1):1-1
11. Redman LM, Ravussin E. Caloric restriction in humans: impact on physiological, psychological, and behavioral outcomes. Antioxidants & redox signaling. 2011 Jan 15;14(2):275-87.
12. Zhang HT, Li LY, Zou XL, Song XB, Hu YL, Feng ZT, Wang TT. Immunohistochemical distribution of NGF,

BDNF, NT-3, and NT-4 in adult rhesus monkey brains. Journal of Histochemistry & Cytochemistry. 2007 Jan;55(1):1-9.
13.Li G, Peskind ER, Millard SP, Chi P, Sokal I, Yu CE, Bekris LM, Raskind MA, Galasko DR, Montine TJ. Cerebrospinal fluid concentration of brain-derived neurotrophic factor and cognitive function in non-demented subjects. PloS one. 2009;4(5).
14. Kaptan Z, Akgun-Dar K, Kapucu A et al (2015) Long term consequences on spatial learningmemory of low-calorie diet during adolescence in female rats; hippocampal and prefrontal cortex BDNF level, expression of NeuN and cell proliferation in dentate gyrus. Brain Res 1618:194–204.
15.Qin W, Chachich M, Lane M et al (2006) Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (Saimiri sciureus). J Alzheimers Dis 10:417–422.
16.Wahl D, Coogan SC, Solon-Biet SM, de Cabo R, Haran JB, Raubenheimer D, Cogger VC, Mattson MP, Simpson SJ, Le Couteur DG. Cognitive and behavioral evaluation of nutritional interventions in rodent models of brain aging and dementia. Clinical interventions in aging. 2017;12:1419.
17.Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, LaFerla FM, Mattson MP. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiology of disease. 2007 Apr 1;26(1):212-20.
18.Shin BK, Kang S, Kim DS, Park S. Intermittent fasting protects against the deterioration of cognitive function, energy metabolism and dyslipidemia in Alzheimer's disease-induced estrogen deficient rats. Experimental Biology and Medicine. 2018 Feb;243(4):334-43.
19.Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences. 2009 Jan 27;106(4):1255-60.
20.Siervo M, Arnold R, Wells JC, Tagliabue A, Colantuoni A, Albanese E, Brayne C, Stephan BC. I ntentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta analysis. Obesity Reviews. 2011 Nov;12(11):968-83.
21.Leclerc E, Trevizol AP, Grigolon RB, Subramaniapillai M, McIntyre RS, Brietzke E, Mansur RB. The effect of caloric restriction on working memory in healthy non-obese adults. CNS spectrums. 2019 Apr 10:1-7.
22.Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nature Reviews Neurology. 2018 Mar;14(3):168.
23.Lieberman HR, Caruso CM, Niro PJ, Adam GE, Kellogg MD, Nindl BC, Kramer FM. A double-blind, placebo-controlled test of 2 d of calorie deprivation: effects on cognition, activity, sleep, and interstitial glucose concentrations. The American journal of clinical nutrition. 2008 Sep 1;88(3):667-76.
24. Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight, and normal weight subjects—a narrative review of human and animal evidence. Behavioral Sciences. 2017 Mar;7(1):4.

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Dureshahwar Kanwar; data collection, data analysis, manuscript writing, manuscript review
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