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Review

Neuroprotective effects of dietary restriction: Evidence and mechanisms

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ABSTRACT

Dietary restriction (DR, in the form of reduced calorie intake or alternate fasting with overall normal energy supply) elicits cell protective responses in nearly all tissues and organs including brain, and extends lifespan in a fashion that is conserved from the simplest model organisms to mammals and non-human primates. Importantly, studies on DR promise to reveal novel strategies to prolong healthspan and prevent age-related disorders in human beings. The present review focuses on the neuroprotective actions of DR as demonstrated by accumulating experimental and encouraging albeit still limited clinical and epidemiological data. Following an overview of the most relevant evidence for the benefit of DR on neurodegenerative disorders and brain aging and damage in animals and human beings, the article will address the major mechanisms currently believed to participate in these effects, at a tissue (antiinflammation, enhanced adult neurogenesis and neuronal plasticity) and cellular (autophagy and mitochondrial biogenesis) level. Then it will "zoom-in" on the molecular circuitries (AMPK/mTOR, Sirtuins, CREB/Sirt1) whereby neuronal cells perceive the reduced availability of nutrients and translate this information into protective adaptive responses. As a further development of this aspect, the emerging connection between cell metabolism and chromatin remodeling will be analyzed, together with its relevance for our understanding of how food intake affects neuronal gene expression and brain health.

Contents

Abbreviations: ACS, acetyl CoA synthase; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; BDNF, brain derived neurotrophic factor; CPT1, carnitine palmitoyl transferase-1; CR, calorie restriction; CREB, cAMP responsive element binding; DG, dentate gyrus; DR, dietary restriction; e/nNOS, endothelial/neuronal nitric oxide synthase; HAT, histone acetyl transferases; HDAC, histone deacetylases; HD, Huntington's disease; IF, intermittent fasting; LTP, long term potentiation; mTOR, mammalian target of rapamycin; NCS, neural stem cells; NO, nitric oxide; NT, neurotrophin; OAADPr, O-acetyl ADP ribose; PD, Parkinson's disease; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1, PPARgamma co-activator 1; ROS, reactive oxygen species; SVZ, subventricular zone.

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1. Introduction: diet, brain health and cognitive aging

Dietary restriction (reduced calorie intake and/or intermittent fasting) has represented for decades the most robust and reliable experimental strategy to extend longevity (average and maximum lifespan) of laboratory animals and investigate the underlying biological mechanisms [1]. The compelling evidence that limiting access to food prolongs lifespan in a strikingly conserved fashion throughout the evolutionary scale (from yeast to mammals and possibly human beings) demonstrates that longevity is subdued to a kind of metabolic regulation, through a complex array of cell autonomous and non cell autonomous (i.e. humoral, hormonal and neuroendocrine) responses yet far from being completely clarified.

Brain aging leads to cognitive impairment and increased susceptibility to age-related chronic neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington disease (HD). Accumulating evidence from clinical and basic research point to a deep connection between metabolic dysregulation and brain function decline during senescence. Accordingly, type 2 diabetes is currently regarded as a major risk factor for incidence and severity of cognitive impairment and/or AD [2–4], and high blood glucose, as monitored by glycosylated hemoglobin (HbA1c), correlates with lower cognitive capacity and changes in hippocampal microstructure also in apparently healthy women [5], indicating that excess nutrient availability may be detrimental to brain function. Conversely, a 30% reduction in calorie intake for a period of 3 months was found to improve memory performance in elderly individuals, in parallel with reduced fasting plasma levels of insulin and inflammatory markers (C-reactive protein). Along similar lines, a very short (4 days) calorie restriction normalized hypothalamic response to glucose in T2D patients. The latter observation is particularly intriguing, since reduced sensitivity to nutrients and/or insulin is believed to represent a potential mechanism for impaired brain function in the context of metabolic disease [6–8].

In keeping with the above findings in humans, three important prospective studies conducted on monkeys (Macacus Rhesus) have confirmed that CR induces in these animals metabolic, physiological and behavioral changes reminiscent of DR effects in simpler model organisms, although with variable effects on lifespan [9–11]. Importantly, aging CR-treated monkeys were found to suffer less severe brain atrophy (an hallmark of the aging brain) compared to controls fed ad libitum. Moreover, additional studies on aged monkeys subdued to CR have revealed a correlation between preservation of brain volume and microstructure with lower iron accumulation [12], lower circulating proinflammatory cytokines [13], improved insulin sensitivity [14], and a reduction of astrogliosis but not of amyloid plaque load [15].

Studies in rodents also support the notion that brain aging and neurodegeneration are tightly linked with metabolic and energy balance. Genetically obese *LepOb* mice develop an accelerated and more severe Alzheimer-like pathology and cognitive deterioration compared to their lean littermates upon transgenic overexpression of a mutant human APP (amyloid precursor protein) [16]. Similar results were obtained in AD-prone mice subdued to a high fat dietary regimen, while caloric restriction exerted protective effects [17,18]. Moreover, both intermittent fasting and calorie restriction were found to ameliorate behavioral deficits in the triple transgenic (3×TgAD) AD mouse model [19]. Interestingly, intermittent fasting did not affect overall food intake and weight gain in C57Bl/6 mice, thus dissociating beneficial effect of dietary restriction on neuronal health and glucose metabolism from calorie intake, at least in this mouse strain [20]. Similar benefits of dietary restriction have also been observed in murine models for other chronic, age-related diseases like Parkinson's (PD) and Huntington's (HD) diseases, as well as in experimental settings of acute brain injury (stroke) or excitotoxicity (epilepsy) [21,22].

While the few examples above and many others reviewed elsewhere [23,24] point to body energy balance as a main regulator of neuronal and brain health (especially in contexts, such as aging and metabolic disease, of excess availability/reduced utilization of nutrients), it has also become clear that the relationship between energy metabolism and brain function is bidirectional in nature; in fact, brain circuitries not only are modified by diet, but also exert, via neuroendocrine factors and autonomic outflow, a central control over nutrient utilization and insulin secretion in the periphery [25–27], and by extension over the whole body response to food availability in terms of energy balance and glucose homeostasis, stress resistance and possibly longevity [28–31] (Fig. 1).

2. Brain response to diet at a supracellular scale: inflammation and brain plasticity

Metabolic and nutritional stimuli modify brain architecture by affecting tissue-scale processes such as inflammation, adult neurogenesis and synaptic plasticity. Those stimuli operate through both cell autonomous regulatory mechanisms (i.e. mediated by direct nutrient effects on neuronal and glial/stromal cell) as well as to humoral, hormonal and paracrine factors that inform brain on the homeostatic and metabolic asset of the whole body and/or the nearby microenvironment (Fig. 1).

2.1. Inflammation

It is increasingly recognized that a condition of systemic, low grade chronic inflammation ("parainflammation") accompanies the aging process and actively contributes to tissue and body senescence [32–34]. Such inflammatory signature is remarkably reminiscent of the one associated with obesity and the related metabolic and cardiovascular disease [35]; accordingly, dysmetabolism and diabetes are age-related disorders that in turn accelerate tissue damage and shorten mammalian lifespan [36].

Recent evidence point to a primary role for brain in the intricate connection linking inflammation, metabolic disease and body aging [37]. Neuroinflammation and microgliosis, affecting both nutrient sensing hypothalamic nuclei (ventroedial, dorsomedial, arcuate) as well as cognitive brain regions, represent shared histopathologic hallmarks for advanced age and obesity/type 2 diabetes in rodents and humans [38–40]. As in other districts, inflammation triggers insulin resistance, which reduces neuronal survival and accelerates neurodegeneration [7,41]. Moreover, hypothalamic inflammation disrupts the brain-driven control of energy and glucose homeostasis, thus triggering a vicious circle that promotes obesity and diabetes [40,42]. Finally, activation of the proinflammatory factor NFkB in hypothalamic neurons of mice inhibits the release of GnRH, a neuroendocrine defect that favors multiorgan decline of aging [30].