

## REVIEW

# Effects of dietary restriction on neuroinflammation in neurodegenerative diseases

Luigi Fontana<sup>1,2,3</sup> , Laura Ghezzi<sup>4,5</sup> , Anne H. Cross<sup>4</sup> , and Laura Piccio<sup>4,6</sup> 

Recent and accumulating work in experimental animal models and humans shows that diet has a much more pervasive and prominent role than previously thought in modulating neuroinflammatory and neurodegenerative mechanisms leading to some of the most common chronic central nervous system (CNS) diseases. Chronic or intermittent food restriction has profound effects in shaping brain and peripheral metabolism, immunity, and gut microbiome biology. Interactions among calorie intake, meal frequency, diet quality, and the gut microbiome modulate specific metabolic and molecular pathways that regulate cellular, tissue, and organ homeostasis as well as inflammation during normal brain aging and CNS neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis, among others. This review discusses these findings and their potential application to the prevention and treatment of CNS neuroinflammatory diseases and the promotion of healthy brain aging.

## Introduction

Dietary restriction (DR) is defined as a chronic or intermittent reduction of food intake without malnutrition. It is the most robust experimental intervention to delay the onset of a wide range of age-associated pathologies and to extend lifespan, as shown in a variety of species (Fontana and Partridge, 2015). Evidence from experimental studies indicates that age-associated accumulation of molecular and cellular damage can be prevented or greatly delayed by dietary, genetic, and pharmacological manipulations that down-regulate key cellular nutrient-sensing and inflammatory pathways (Fontana et al., 2010b). Health-promoting actions of DR include metabolic, antioxidant, and immunomodulatory adaptations that could potentially influence the initiation, progression, and prognosis of a range of neurological and neuroinflammatory disorders.

Neuroinflammation is a coordinated response of the central nervous system (CNS) to harmful stimuli and injuries, including those occurring during infections, traumatic brain injury, or other neurological diseases. It is characterized by activation and proliferation of the two major CNS glial cells, microglia and astrocytes, which undergo morphological changes and release proinflammatory mediators (cytokines, chemokines, and complement proteins; Matias et al., 2019; Wolf et al., 2017). Often, neuroinflammation is associated with increased blood-brain barrier permeability, allowing immune cell trafficking and

soluble proinflammatory factors to enter the CNS, where they can directly interact with glial and neuronal cells and contribute to the inflammatory process. The goal of inflammatory and immune responses is to clear the hazard. When this is achieved, activation of anti-inflammatory pathways then offsets the inflammatory process to restore tissue integrity and function. If the precipitating factors are persistent (as in some neurodegenerative diseases), chronic neuroinflammation may ensue. Chronic neuroinflammation has been proposed as a potential deleterious mediator of aging, as well as other pathological conditions (Di Benedetto et al., 2017). Increasing evidence supports the involvement of chronic neuroinflammation in the pathogenesis of neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), as well as in multiple sclerosis (MS), a more classic neuroinflammatory disease (Stephenson et al., 2018).

Recent advances are highlighting the complex relationship between nutrient metabolism and the activation of inflammatory pathways in different tissues including the brain. Notably, disruption of brain energy metabolism with reduced glucose consumption, increased central insulin resistance, and impaired mitochondrial function have been linked to the mechanisms leading to neuroinflammatory and age-related neurodegenerative diseases (Cunnane et al., 2020; Zilberter and Zilberter, 2017). This evidence prompted the hypothesis that reestablishing metabolic

<sup>1</sup>Charles Perkins Center, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; <sup>2</sup>Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia; <sup>3</sup>Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy; <sup>4</sup>Department of Neurology, Washington University in St. Louis, St. Louis, MO; <sup>5</sup>University of Milan, Milan, Italy; <sup>6</sup>Brain and Mind Centre, School of Medical Sciences, University of Sydney, Sydney, New South Wales, Australia.

Correspondence to Laura Piccio: [laura.piccio@sydney.edu.au](mailto:laura.piccio@sydney.edu.au).

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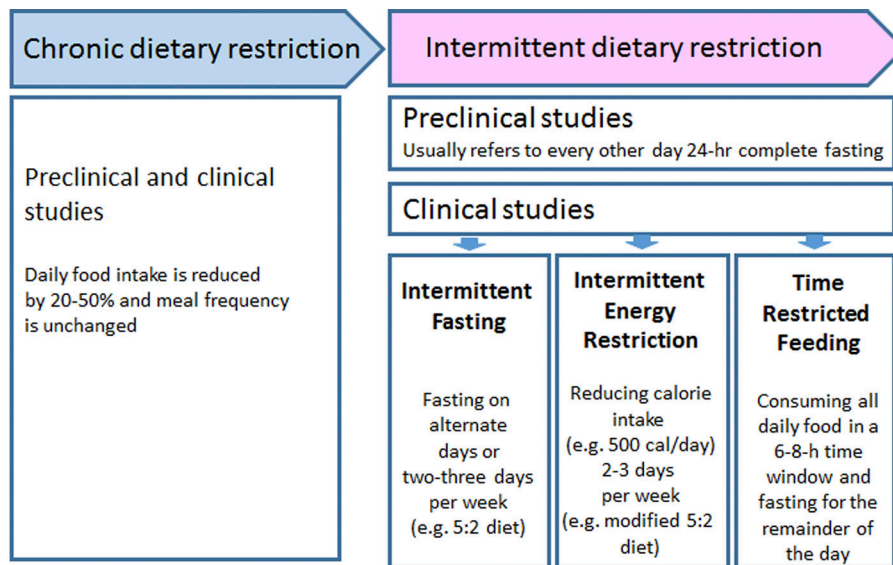


Figure 1. **Types of DR in preclinical and clinical studies.** Description of the main characteristics of chronic and intermittent DR regimens used in preclinical animal studies and clinical studies in humans.

balance could be a key intervention to counteract underlying disease processes. DR could potentially serve this purpose by exerting its effects on metabolic and anti-inflammatory pathways. This review article aims to summarize current evidence regarding the effects of DR on neuroinflammation and the potential central and systemic underlying mechanisms. Major studies that tested the effects of DR in experimental models, epidemiological studies, and clinical trials for various neurodegenerative disorders in which neuroinflammation may play a role are discussed.

### Methods of DR

DR can be achieved by chronically reducing food intake or by changing meal frequency and timing (Fig. 1). In chronic DR, daily food intake is reduced by 20–50%, but meal frequency is unchanged. In contrast, with intermittent fasting (IF), food intake is completely eliminated or greatly reduced intermittently, for example, every other day. In humans, moderate 20–30% chronic DR has been tested long-term in clinical trials and observational studies (Most et al., 2017) or during episodes of involuntary energy intake reduction (Hindhede, 1920; Strom and Jensen, 1951). IF in experimental models usually refers to every-other-day 24-h complete fasting, while in humans it refers to a variety of approaches including fasting or calorie restriction (e.g., 500 calories per day) on alternate days or 2 d per week (5:2 diet), or skipping breakfast and lunch  $\geq 2$  d each week (Patterson et al., 2015). Another form of intermittent DR is time-restricted feeding, which involves consuming all daily food in a 4- to 6-h time window and fasting for the remainder of the day (Cienfuegos et al., 2020; Fig. 1). Evidence from clinical and animal studies suggests that chronic DR and IF affect lifespan and age-associated diseases via similar metabolic and molecular mechanisms (Hadem et al., 2019; Mattson et al., 2014).

### Mechanisms mediating anti-inflammatory effects of DR

Central and systemic effector mechanisms contribute to CNS neuroinflammation. Central mechanisms are driven by primary CNS insults (e.g., brain injury, protein deposition, or accumulation

of senescent cells), inducing inflammatory responses involving resident or infiltrating immune cells. CNS inflammation can also be induced or potentiated by peripheral factors such as systemic inflammatory mediators reaching the CNS, insulin resistance, and other metabolic conditions (e.g., obesity or dyslipidemia), leading to activated microglia and astrocytes (Lee and Mattson, 2014; Mattson and Arumugam, 2018). Environmental factors (e.g., diet, physical inactivity, smoke/pollution, or mental stress) can play a key role in triggering central or systemic mechanisms leading to CNS inflammation. Recent advances have recognized a prominent role in the connections between the periphery and the brain of the gut–brain axis, which is the bidirectional communication between the central and the enteric nervous systems linking gut functions with emotional and cognitive centers in the brain. A primary role in this complex cross-talk is played by the gut microbiota through neural, endocrine, immune, and humoral mechanisms partially mediated by the vagus nerve and the parasympathetic nervous system (Fig. 2). In this scenario, DR elicits protective changes in the gut microbiota composition, with metabolic and molecular adaptations in nearly all tissues and organs including the brain. Thus, DR can potentially modulate both central and peripheral factors contributing to neuroinflammation. The main adaptations induced by DR on metabolic and neuroinflammatory pathways are discussed in this section and summarized in Fig. 3.

### Reduced adiposity

Adipose tissue is a major source of cytokines and hormones, collectively known as “adipokines,” which can modulate multiple immune and metabolic responses (Fontana et al., 2007; Lee et al., 2019). DR powerfully reduces adiposity, especially visceral adiposity (Das et al., 2017; Racette et al., 2006), resulting in diminution of fat-derived cytokines and other proinflammatory mediators and increase of anti-inflammatory molecules such as IL-10 (Ma et al., 2020; Willette et al., 2013). In experimental models, DR reduces the proinflammatory adipokine leptin and increases adiponectin, which has insulin-sensitizing and anti-inflammatory effects (Higami et al., 2004). In humans, DR

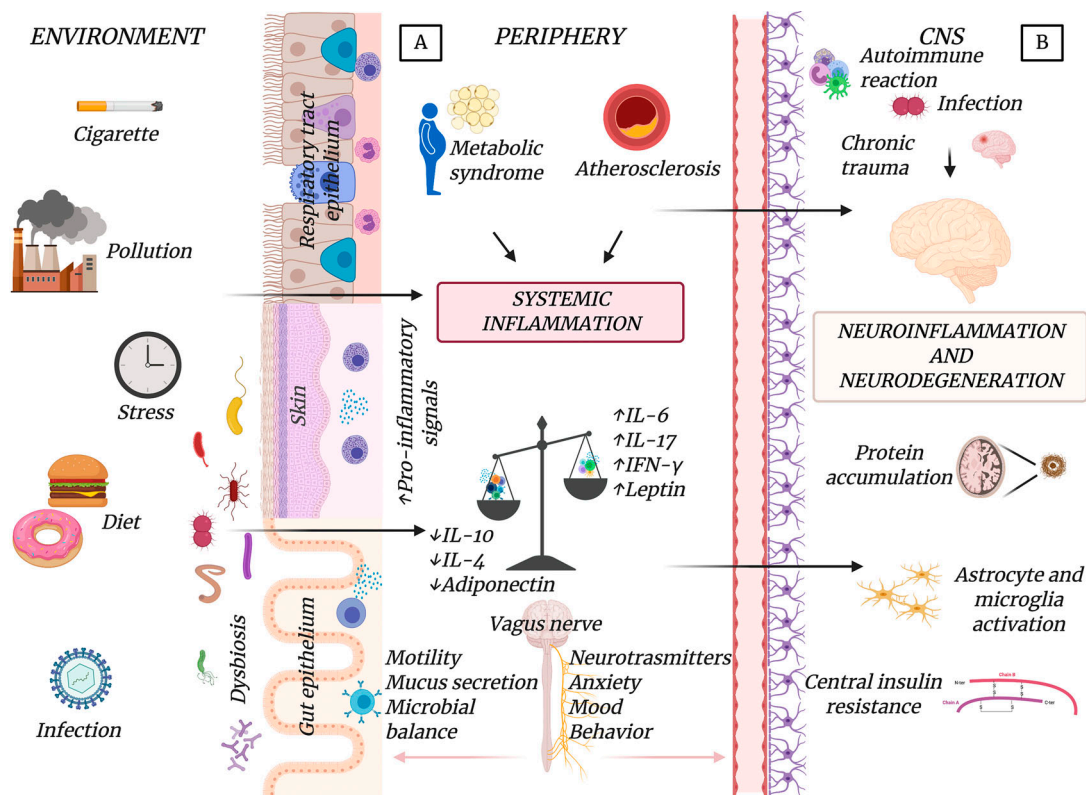


Figure 2. **Central and peripheral mechanisms leading to neuroinflammation.** (A and B) Neuroinflammation with activation of microglia and astrocytes in the CNS could be induced by peripheral (A) or central (B) effector mechanisms. Environmental factors (diet, infections, pollution, etc.) can have effects on the gut microbiota (e.g., gut dysbiosis or increased permeability) or other epithelial barriers, and then cause peripheral metabolic and immune-inflammatory responses (e.g., metabolic syndrome or atherosclerosis) responsible for systemic inflammation. This contributes to CNS inflammation, which could also be evoked by central processes (e.g., chronic trauma, autoimmune attacks, or infections). The parasympathetic system through the vagus nerve mediates the cross-talk between the periphery and the CNS and may modulate neuroinflammation.

induces similar changes in serum adipokines (Fontana et al., 2010a). Reduction of abdominal fat in humans was associated with lower levels of C-reactive protein, TNF- $\alpha$ , and F2-isoprostanes, markers of systemic inflammation and oxidative stress (Il'yasova et al., 2018; Meydani et al., 2016). Mechanistically, adipokines are important nodes integrating immunometabolic pathways and controlling T cell effector functions. Leptin, as well as insulin signaling, supports T cell metabolic (nutrient uptake and glycolytic and respiratory capacities) and immune responses leading to the production of proinflammatory cytokines IFN- $\gamma$  and TNF- $\alpha$  (Saucillo et al., 2014; Tsai et al., 2018) and the response to pathogens (Ganeshan and Chawla, 2014).

#### Improved insulin sensitivity and reduced advanced glycation end-product (AGE) formation

Brain aging, AD, and other neuroinflammatory diseases are associated with insulin resistance, microgliosis, and elevated inflammatory markers (IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ) in the brain, cerebrospinal fluid, and plasma (Akiyama et al., 2000; Craft and Watson, 2004; Pekkala et al., 2020). In the Rotterdam study, a twofold increase in baseline insulin or insulin resistance corresponded to a 40% greater likelihood of AD conversion among participants without type 2 diabetes and doubling of the risk in diabetic patients (Schrijvers et al., 2010). Chronic DR in rodents

and humans improves insulin sensitivity and glucose tolerance (Kraus et al., 2019; Weiss et al., 2006; Yoshino et al., 2020), thus reducing formation of AGEs that interfere with normal cell function (Cefalu et al., 1995; Fontana et al., 2010a; Kraus et al., 2019; Masoro et al., 1989; Weiss et al., 2006). AGEs exert their detrimental actions by binding specific receptors called RAGEs (receptors for AGEs), widely expressed on many cells including neural and immune cells. RAGE activation elicits up-regulation of proinflammatory cytokines (e.g., TNF- $\alpha$  and IL-1) and rapid generation of reactive oxygen species (Jiang et al., 2018; Vlassara et al., 2002), and it has been implicated in the pathogenesis of diabetes, atherosclerosis, and neuroinflammation and potentially in many CNS diseases (Ashraf et al., 2015; Basta, 2008; Wang et al., 2020).

#### Increased glucocorticoid production and antistress pathways

In rodents, chronic DR and IF have been consistently associated with increased circulating levels of endogenous corticosteroids, hormones with potent anti-inflammatory and immunomodulatory activities. As in animals, long-term DR in humans is associated with sustained rises in serum cortisol (Fontana et al., 2016). In people strictly practicing 30% DR for 3–15 yr, serum cortisol was ~30% higher than in age-matched sedentary controls and endurance athletes, and inversely correlated with



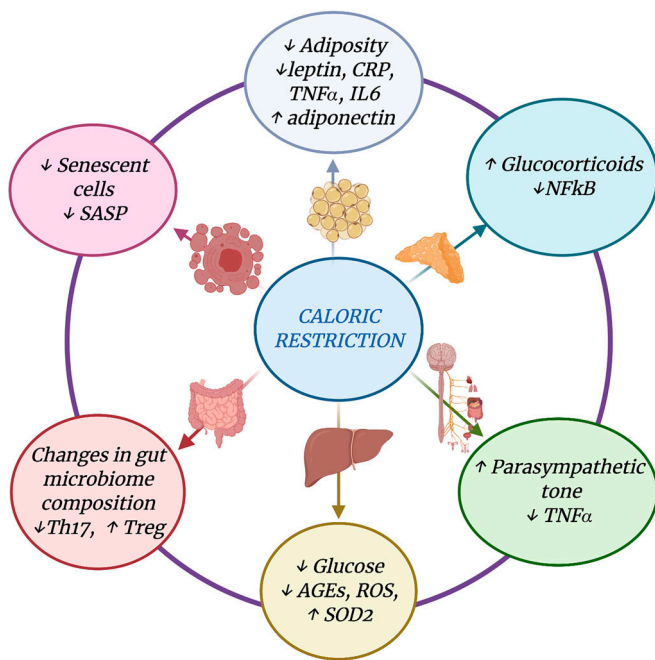


Figure 3. **Mechanisms mediating DR anti-inflammatory effects.** Main adaptations induced by DR on metabolic, hormonal, gut microbiota, and immune/inflammatory pathways. AGEs, advanced glycation end products; CRP, C-reactive protein; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SOD2, superoxide dismutase 2.

serum levels of TNF- $\alpha$  (Yang et al., 2016). In the latter study, DR was associated with reduced transcripts of several inflammatory mediators in skeletal muscle, including NF- $\kappa$ B, STAT5, inducible nitric oxide synthase, TNF- $\alpha$ , IL-6, and IL-8. Furthermore, DR was associated with a significant increase in key stress-related molecular chaperones (HSP-70 and Grp78) and autophagic (LC3 and beclin-1) mediators involved in cellular protein quality control and removal of dysfunctional proteins and organelles (Yang et al., 2016).

#### Reduction of senescent cells and senescence-associated secretory phenotype (SASP)

Another mechanism through which DR may inhibit inflammation is by reducing the accumulation of senescent cells during aging (Fontana et al., 2010a). Cellular senescence is a potent tumor-suppressive mechanism that inhibits the proliferation of cells at risk for malignant transformation, but at the same time induces the secretion of a range of growth factors, metalloproteinases, proinflammatory cytokines, and chemokines, collectively named SASPs (Chinta et al., 2015; Coppé et al., 2010). Cell senescence can be prematurely induced by several insults, including cellular damage caused by metabolic dysfunction, oxidative stress, genotoxic stress, and overactivation of oncogenes or loss of some tumor suppressor genes (Borghesan et al., 2020; McHugh and Gil, 2018). Accumulating evidence suggests that the chronic inflammatory SASP environment contributes to brain aging and to the development of age-associated diseases, including AD (Ovadya and Krizhanovskiy, 2014). Recent studies

have linked tau-dependent pathology to cellular senescence and failure to clear senescent glial cells (Bussian et al., 2018; Musi et al., 2018). Astrocytes help to maintain glutamate homeostasis in the brain by removing extracellular glutamate via excitatory amino acid transporters. Astrocyte senescence may provoke glutamate toxicity in cortical neurons, which causes and enhances neurodegeneration and neuroinflammation (Limbad et al., 2020). Several DR animal studies as well as long-term DR in humans have shown that DR was associated with reduced senescent cell markers in multiple tissues (Fontana et al., 2010a).

#### Activation of the parasympathetic anti-inflammatory pathway

The autonomic nervous system regulates important body functions such as heart rate, blood pressure, and gastrointestinal motility, but it also modulates systemic inflammation (Pavlov and Tracey, 2012; Salama et al., 2020). Stimulation of the parasympathetic nervous system (efferent vagus nerve) inhibits TNF- $\alpha$  synthesis by macrophages, reduces serum TNF- $\alpha$  during endotoxemia, and prevents development of shock (Borovikova et al., 2000). In contrast, vagotomy intensifies TNF- $\alpha$  activity and amplifies the response to endotoxemia. By binding to the macrophage  $\alpha 7$  nicotinic acetylcholine receptor, the neurotransmitter acetylcholine (released by the efferent vagus nerve endings) is responsible for the reduced secretion of TNF- $\alpha$  by human macrophages (Wang et al., 2003). Rodent studies have shown that DR increases the high-frequency component of the heart rate variability spectrum, a marker of parasympathetic activity (Mager et al., 2006). Similarly, long-term DR without malnutrition in humans increased parasympathetic activity as measured by heart rate variability (Stein et al., 2012).

#### Enhanced gut microbiota-dependent anti-inflammatory pathways

Another mechanism through which DR may induce beneficial metabolic and anti-inflammatory effects involves alterations of gut microbiota composition and function (Estrada and Contreras, 2019). The gut microbiota plays a crucial role in maintaining a symbiotic relationship with the host and regulates several important functions, including host metabolism and intestinal and systemic immune inflammatory responses (Rooks and Garrett, 2016). Life-long DR in mice is known to change the gut microbiota structure with enrichment of anti-inflammatory bacteria strains such as the genus *Lactobacillus*, accompanied by reduced serum proinflammatory endotoxin load from the gut (Zhang et al., 2013). In a different study in naive mice, every-other-day fasting altered the gut microbiota composition by increasing levels of Firmicutes and the production of short-chain fatty acids, which are known to have immunomodulatory and anti-inflammatory effects (Li et al., 2017). We showed that 1 mo of IF led to increased gut bacteria diversity, with enrichment of the Lactobacillaceae, Bacteroidaceae, and Prevotellaceae families and associated enhancement of several antioxidative microbial metabolic pathways. These changes were associated with increased frequencies of gut-associated regulatory T cells and decrease of IL-17-producing T cells (Th17; Cignarella et al., 2018).

In humans, long-term DR was shown to increase gut microbiota richness and diversity, characteristics referring to the

number of bacterial species (based on total bacterial gene counts) in the gut and of individual bacteria within each species, respectively. High microbiota richness is associated with improved metabolic health (reduced adiposity; lower leptin, insulin, and triglycerides; and higher adiponectin and HDL cholesterol levels) and reduced inflammation (lower C-reactive protein and white blood cell counts; [Le Chatelier et al., 2013](#)). One study showed that the gut microbiota of individuals practicing chronic DR were significantly more diverse when compared with individuals on a typical Western diet ([Griffin et al., 2017](#)). Another study showed that an energy-restricted diet increased gut bacteria richness in individuals classified as having “low gene counts” and was associated with reduced adiposity and improved insulin sensitivity, as well as a trend toward a reduction of systemic inflammation, as evidenced by decreased C-reactive protein levels ([Cotillard et al., 2013](#)).

### Effects of DR on normal aging and neurodegenerative diseases

Numerous studies have explored DR effects in normal brain aging as well as chronic neuroinflammatory and neurodegenerative diseases. Most of the long-term studies were conducted in rodents and monkeys. Human studies have mainly been relatively short-term trials testing the effects of the diet primarily on systemic metabolic conditions. In the following section, we review the main published studies on the effects of DR on normal aging and neurodegenerative diseases (summarized in [Table 1](#)) in which systemic and brain inflammation plays a prominent role.

#### Normal aging

Aging is associated with systemic low-grade chronic inflammation (called “inflammaging”) that also involves the brain ([Franceschi et al., 2018](#)). Neuroinflammation accompanies the age-related decline of brain function ([Di Benedetto et al., 2017](#)) and involves activated brain glial cells. Upon aging, MHCII expression by microglia and glial fibrillary acidic protein (GFAP) expression by astrocytes are increased ([Morgan et al., 1999](#); [Wong, 2013](#)). Acquisition of a senescent phenotype by microglia may also contribute to the development of age-associated neurodegenerative diseases ([Streit, 2004](#); [Wong, 2013](#)).

Several lines of evidence have shown that DR exerts beneficial effects against age-driven neuroinflammation. In rodents, DR attenuated age-dependent astrocyte and microglia activation in the brain ([Kaur et al., 2008](#); [Morgan et al., 1999](#); [Yin et al., 2018](#)). Long-term DR in aged mice inhibited a number of inflammatory genes in the neocortex and cerebellum by inducing a type I interferon response and suppressing NF- $\kappa$ B signaling and oxidative stress pathways ([Lee et al., 2000](#)). Similarly, short-term IF ameliorated age-associated decrease in motor and cognitive performance in rats by enhancing mitochondrial complex IV activity and reducing oxidative molecular damage ([Singh et al., 2012](#)). The effects of DR on brain aging in rodents are discussed in more detail in a recent review by [Hadem et al. \(2019\)](#).

Data on DR effects on neuroinflammation in nonhuman primates are accumulating. Most published reports have examined DR neuroprotective effects on neuroimaging biomarkers

or brain pathology. Results from the Wisconsin National Primate Research Center (WNPRC) study showed that moderate chronic DR (30% reduced intake from individualized baseline), initiated in young adulthood, reduces age-associated gray matter brain atrophy in several key cerebral regions of rhesus macaques compared with animals fed ad libitum ([Colman et al., 2009](#)). In the same WNPRC study, chronic DR led to a significant reduction of astrogliosis (measured as levels of GFAP expression) in the hippocampus and iron accumulation (measured by brain magnetic resonance imaging [MRI]) in the basal ganglia and cortical areas ([Kastman et al., 2012](#); [Sridharan et al., 2013](#)); these changes were associated with improved performance on executive and motor function tests in the DR, but not in the control group ([Sridharan et al., 2012](#)). Moreover, chronic DR in non-human primates improved insulin sensitivity and lowered blood proinflammatory cytokine concentrations, which were associated with more gray matter volume in the hippocampus and more white matter volume primarily in visual areas and the dorsal prefrontal cortex ([Willette et al., 2010, 2012](#)). Another lifelong study in squirrel monkeys found that 30% DR reduced levels of amyloid  $\beta$  ( $A\beta$ )<sub>1–40</sub> and  $A\beta$ <sub>1–42</sub> peptides in the temporal cortex in association with elevation of  $\alpha$ -secretase activity ([Qin et al., 2006](#)).

Chronic metabolic disorders (e.g., obesity, dyslipidemia, and insulin resistance) associated with systemic inflammation accelerate brain aging ([Cunnane et al., 2020](#); [Mattson and Arumugam, 2018](#)). Cognitive performance of metabolically morbid individuals is poorer than their age-matched healthy counterparts ([Kullmann et al., 2016](#)). Several epidemiological studies have reported that obesity and metabolic syndrome in midlife are associated with impaired cognitive function ([Debetto et al., 2011](#)). A population-based cohort study of cognitively healthy participants suggested that high visceral adiposity and systemic inflammation were associated with deep white matter brain hyperintensities, reduced gray matter volume (measured by MRI), and potentially with reduced executive functions ([Lampe et al., 2019](#)).

In humans, studies of chronic DR have reported beneficial effects on metabolic factors and cognitive functioning in healthy volunteers and obese and hypertensive patients. A 3-mo interventional study of 30% DR in healthy, normal-weight to overweight elderly subjects showed significant improvement in memory performance, with concomitant reductions in fasting insulin and C-reactive protein levels ([Witte et al., 2009](#)). Similar results have been reported for a younger population of nonobese (body mass index [BMI] 22–28 kg/m<sup>2</sup>) men and women enrolled in the large National Institute on Aging-funded multicenter randomized trial Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE). At the end of the second year, the volunteers randomized to 25% DR experienced a better performance in working memory tests than the control group ([Leclerc et al., 2020](#)). In the Exercise and Nutrition Intervention for Cardiovascular Health (ENCORE) trial, 3 mo of exercise training coupled with an energy-restricted Dietary Approaches to Stop Hypertension (DASH) diet (high in low-fat dairy products, fruits, vegetables, and fiber and low in fats; [Appel et al., 1997](#)) resulted in a significant improvement of

Table 1. Preclinical and clinical studies on DR in aging and neurodegenerative diseases

Model	Reference	Type of DR	DR effects on inflammatory or other brain pathology markers	DR effects on cognitive or motor functions	DR effects on imaging measures
<b>Aging</b>					
Rodents	Morgan et al., 1999; Lee et al., 2000	30–40% DR	↓ Age-related increased of activation markers on microglia (e.g., MHCII) or astrocytes (e.g., GFAP); ↓ inflammatory genes		
	Kaur et al., 2008	IF	↓ Age-related changes in brain expression of NCAM, PSA-NCAM, and GFAP		
	Singh et al., 2012	IF	↓ Protein oxidative damage; ↑ markers of synaptic plasticity in the hippocampus	Ameliorates motor coordination, cognitive skills	
Nonhuman primates	Qin et al., 2006	30% DR	↓ Aβ deposition		
	Willette et al., 2010	30% DR	Attenuates the relation between IL-6 and brain volume loss		Attenuates the relation between IL-6 and brain volume loss
	Willette et al., 2012	30% DR	Attenuates the negative correlation between homocysteine and global gray matter volume		Attenuates the negative correlation between homocysteine and global gray matter volume
	Colman et al., 2009; Kastman et al., 2012; Sridharan et al., 2012; Sridharan et al., 2013	30% DR (University of Wisconsin study)	↓ Age-related astrogliosis (↓ GFAP in hippocampus and entorhinal cortex)	Preserves motor performance	No effect on corpus callosum integrity; ↑ FA in several white matter regions; ↓ GM volume loss; ↓ brain iron accumulation
	Leclerc et al., 2020; Witte et al., 2009	25–30% DR		Ameliorates memory performance	↓ C reactive protein and insulin levels
Humans	Blumenthal et al., 2010; Smith et al., 2010	DASH diet (Appel et al., 1997) and DR		Improves cognitive function	
<b>AD</b>					
Rodents	Patel et al., 2005; Wang et al., 2005; Wu et al., 2008; Schafer et al., 2015	30–40% DR	↓ Aβ and phospho-tau deposition; ↓ astrocyte activation	Improved performance in cognitive tests	
	Halagappa et al., 2007; Brownlow et al., 2014	Different DR regimens based on individual calorie consumption; 35–40% DR	No effects	Improved age-related behavioral impairments; rescued associative memory deficits	
Humans	Horie et al., 2016	DASH diet + DR 500 kcal/d or 25% DR		Improvement in cognitive functions	
<b>PD</b>					
Rodents	Duan and Mattson, 1999	IF	↓ Damage to SN neurons	↓ Motor deficits	
	Maswood et al., 2004	30% DR	↑ Levels of dopamine and dopamine metabolites in the striatal region	↑ Locomotor activity	No differences in presynaptic dopaminergic activity in vivo
	Armentero et al., 2008	IF	No effect on nigrostriatal degeneration		
	Griffioen et al., 2013	IF	NA	Ameliorates autonomic function	NA

Table 1. Preclinical and clinical studies on DR in aging and neurodegenerative diseases (Continued)

Model	Reference	Type of DR	DR effects on inflammatory or other brain pathology markers	DR effects on cognitive or motor functions	DR effects on imaging measures
Nonhuman primates	Maswood et al., 2004	30% DR	↑ Levels of dopamine and dopamine metabolites in the striatal region	↑ Locomotor activity	No differences in presynaptic dopaminergic activity in vivo
<b>ALS</b>					
Rodents	Pedersen and Mattson, 1999	IF		Accelerates disease onset and shortens disease duration	
	Hamadeh et al., 2005	40% DR		Accelerates disease onset	
<b>MS</b>					
Rodents	Esquifino et al., 2007	66%	Alters lymphocytes composition in lymphoid organs, ↓ IFN- $\gamma$ production	Prevents EAE	
	Piccio et al., 2008	40% DR	↑ Corticosterone and adiponectin; ↓ leptin and IL-6	Ameliorates EAE clinical course	
	Kafami et al., 2010	IF		Ameliorates EAE clinical course and reduces incidence of disease	
	Cignarella et al., 2018	IF	↓ Th17 cells, ↑ T regulatory cells in small intestine lamina propria, altered gut microbiota	Ameliorates EAE clinical course and reduces incidence of disease	
	Jordan et al., 2019	IF	↓ Monocyte infiltration in the spinal cord, ↓ <i>TNF<math>\alpha</math></i> , <i>IL-1<math>\beta</math></i> , <i>CXCL2</i> , and <i>CXCL10</i>	Ameliorates EAE clinical course and reduces incidence of disease	
Humans	Saadatnia et al., 2009	Ramadan fasting		Well tolerated, no differences in relapse rate	
	Etemadifar et al., 2016	Ramadan fasting		Improves physical health and mental health composites of QOL	
	Choi et al., 2016	FMD + Mediterranean or ketogenic diet		Improves QOL	
	Fitzgerald et al., 2018	22% DR or IF		Improves mood	
	Cignarella et al., 2018	IF	↓ Leptin		

Summary of the main studies on the effects of DR on aging and neurodegenerative and neuroinflammatory diseases. FA, fractional anisotropy. GM, gray matter; NA, not applicable; NCAM, neural cell adhesion molecule; PSA, polysialylated; QOL, quality of life; SN, substantia nigra.

cognitive function in hypertensive individuals (Blumenthal et al., 2010; Smith et al., 2010).

#### AD

AD brain pathology is characterized by abnormal accumulation of A $\beta$  plaques, aggregated hyperphosphorylated tau in neurofibrillary tangles, and neuroinflammation. These pathological hallmarks are also observed in normal brain aging, but in AD they progress much faster and to a greater extent. Systemic inflammation and insulin resistance are emerging as important drivers of AD progression (Heneka et al., 2015; Heppner et al., 2015).

Several studies have demonstrated beneficial effects of DR or IF on brain pathology and functional outcomes in AD transgenic

rodent models (Table 1). Short- and long-term DR decreased or prevented A $\beta$  accumulation in the hippocampus and cerebral cortex of transgenic mice carrying familial AD amyloid-precursor protein mutations (Patel et al., 2005; Schafer et al., 2015; Wang et al., 2005) and attenuated A $\beta$  plaque-associated astrogliosis (Patel et al., 2005; Wu et al., 2008). In mouse models with tau deposition (alone or combined with A $\beta$ ), long-term DR improved cognitive and behavioral performance, with inconsistent effects on A $\beta$  and phospho-tau levels in the hippocampus (Brownlow et al., 2014; Halagappa et al., 2007). In triple-transgenic mouse models of AD, an IF regimen has been associated with increased neuronal differentiation in the hippocampus (Li et al., 2020). A comprehensive review of these studies has been recently published (Bok et al., 2019).



Epidemiological data suggest a relationship between calorie intake, obesity, and dementia risk. A prospective study of a large cohort of elderly individuals free of dementia at baseline provided evidence that those with a lower calorie intake had a reduced risk of developing AD (Luchsinger et al., 2002). Obesity at midlife increases the risk of AD, as shown in a population-based cohort study with an average 21-yr follow-up. In this study, clustering of vascular risk factors (high total cholesterol and high blood pressure) increased the risk in an additive manner (Kivipelto et al., 2005). Other epidemiological studies suggest a strong association between high blood pressure and late-life dementia (Ding et al., 2020), and the SPRINT MIND trial demonstrated that reducing systolic blood pressure to <120 mm Hg compared with <140 mm Hg significantly reduced the risk for mild cognitive impairment (MCI) and dementia (Williamson et al., 2019). In an 18-yr follow-up study of nondemented women, being overweight at age 70 was associated with a higher risk of developing dementia later in life; for every 1.0 unit of BMI increment in women aged 70–75 yr, AD risk increased by 36% at 79–88 yr of age (Gustafson et al., 2003). Preliminary data from randomized controlled trials are supportive of a cause–effect relationship. In one small 12-mo trial of 80 obese patients with MCI, aged ≥60 yr, weight loss was associated with improvements in verbal memory, verbal fluency, executive function, and global cognition (Horie et al., 2016). In this study, improvements in insulin resistance and inflammation were associated with better cognitive tests. More randomized trials on the effects of DR in individuals with subjective memory complaints and MCI are currently ongoing.

## PD

PD, the second most common human CNS neurodegenerative disease, is characterized by progressive debilitating motor and nonmotor symptoms. Accumulation of  $\alpha$ -synuclein aggregates within neurons causes neuronal loss primarily in the substantia nigra (Braak et al., 2003; Mendoza-Velázquez et al., 2019). Postmortem brain pathology of PD patients reveals inflammatory changes in microglia (McGeer et al., 1988). Activation of microglia by  $\alpha$ -synuclein aggregates resulting in inflammatory and oxidative damage of neurons is one of the main culprits in PD pathogenesis (Hoenen et al., 2016; Hoffmann et al., 2016). One novel compelling hypothesis is that  $\alpha$ -synuclein pathology originates in the gastrointestinal tract and is transmitted to the brain via the vagus nerve (Braak et al., 2003; Kim et al., 2019; Van Den Berge et al., 2019).

Preclinical data suggest a potential role of diet and DR in the progression of PD. High-fat diet-induced obesity can increase the vulnerability of dopaminergic neurons of the substantia nigra in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD (Choi et al., 2005), whereas IF and 30% DR attenuated MPTP-induced neurotoxicity in both mouse and nonhuman primate models (Duan and Mattson, 1999; Maswood et al., 2004). These results were not confirmed in a 6-hydroxydopamine model of PD, in which IF did not prevent nigrostriatal degeneration (Armentero et al., 2008). IF can ameliorate autonomic dysfunction in a PD transgenic mouse model (Griffioen et al., 2013), and growing evidence suggests

that modifications of gut microbiota may be involved in the development of motor symptoms and  $\alpha$ -synuclein inclusions in the CNS of PD mouse models. Remarkably, transplantation of microbiota from PD-affected patients into  $\alpha$ -synuclein-overexpressing mice enhanced motor dysfunction, suggesting that dietary manipulation of the human gut microbiome may play a role in the treatment of PD (Sampson et al., 2016).

Little is known on the effects of diet and DR on PD development and progression in humans. Some epidemiological studies suggest a relationship between BMI and PD risk (Hu et al., 2006), but others did not confirm this association (Roos et al., 2018). Being underweight might even have a negative effect by increasing the risk of PD, especially in patients with diabetes mellitus (Jeong et al., 2020). No randomized clinical trials of the effects of DR or fasting on PD progression have been published so far. However, it is interesting to note that people with PD display lower levels of ghrelin compared with healthy controls, even when matched by BMI (Fiszer et al., 2010). In a mouse model of PD, ghrelin exerted neuroprotective effects during 30% DR through the attenuation of MPTP-induced nigrostriatal damage and loss of dopaminergic neurons (Bayliss et al., 2016). Prolonged DR and fasting powerfully increases plasma concentrations of ghrelin (Hoddy et al., 2016), a “hunger hormone” with anti-inflammatory functions (Dixit et al., 2004).

## ALS

ALS is a fatal neurodegenerative disease, causing motor neuron death and progressive muscle paralysis. Approximately 85–90% of cases are sporadic; the remaining 10–15% are classified as familial, with Cu/Zn superoxide dismutase 1 (SOD1) mutations accounting for ~30% of them (Rosen et al., 1993). CNS pathology has been extensively studied in SOD1 mutation carriers and SOD1 mutant animal models. Although neuroinflammation may accelerate neuronal death (Boillée et al., 2006), preclinical data suggest a detrimental effect of DR on ALS. An early study from the late 1990s reported that Cu/Zn SOD mutant mice undergoing IF experienced earlier disease onset and shorter disease duration compared with mice fed ad libitum (Pedersen and Mattson, 1999). Another study found that 40% DR accelerates disease onset and progression (Hamadeh et al., 2005). Although the exact mechanism is not known, it seems that DR in the SOD1<sup>G93A</sup> animal model of ALS increases lipid peroxidation, inflammation, and apoptosis in the skeletal muscle, probably by decreasing mitochondrial bioenergetic efficiency and impairing stress response (Patel et al., 2010). To the best of our knowledge, no human studies on the effects of DR on ALS exist.

## MS

MS is an inflammatory demyelinating human disease, presumed to be autoimmune, with varying degrees of axonal and neuronal damage (Wallin et al., 2019). Several studies have shown that obesity during childhood/young adulthood is a risk factor for MS development (Hedström et al., 2012; Langer-Gould et al., 2013; Munger et al., 2009, 2013; Wesnes et al., 2015) and could influence the response to therapy (Huppke et al., 2019). A protective effect of DR in the main animal model of MS, experimental autoimmune encephalomyelitis (EAE), was reported



in 2004. Severe DR, 66% below ad libitum intake, for 15 d before immunization prevented clinical manifestations in the rat EAE model. In this study, DR caused major reductions in circulating growth hormone and increased prolactin levels; depressed lymphocyte responses, such as to the mitogen concanavalin A (Esquifino et al., 2004), and reduced IFN- $\gamma$  production in lymphoid tissues were also reported (Esquifino et al., 2007). Similarly, our group has shown that 40% chronic DR greatly reduced murine EAE severity, in concert with increased endogenous serum corticosterone (the main glucocorticoid hormone in mice) and adiponectin, and decreased serum leptin levels (Piccio et al., 2008). An IF regimen started before disease induction showed similar reductions of murine EAE incidence and severity (Cignarella et al., 2018; Kafami et al., 2010). Additional studies suggested a potential role of the gut microbiome in mediating some of these protective effects. We observed *Lactobacilli* species enrichment, with reduced Th17 cells and increased regulatory T cells in the small intestine lamina propria of mice undergoing IF (Cignarella et al., 2018). Transfer of gut microbiota from these mice inhibited EAE in recipients immunized to induce EAE (Cignarella et al., 2018).

Jordan et al. (2019) have independently confirmed a protective role of IF in the murine EAE model and demonstrated decreased mobilization of monocytes from bone marrow with reduced CNS monocytes and expression of TNF- $\alpha$ , IL-1 $\beta$ , MMP9, CXCL10, and CXCL2 inflammatory mediators. Notably, IF did not inhibit the ability of monocytes to mobilize and function during acute infection or wound healing, suggesting that this strategy might not compromise responses to infection or tissue repair. Indeed, a randomized clinical trial in nonobese men and women demonstrated that prolonged DR markedly reduced inflammation without impairing cell-mediated immunity (Meydani et al., 2016).

Preliminary data suggest that other forms of fasting might have an effect in the EAE model. Three cycles of a fasting mimicking diet (FMD), involving a very-low-calorie and protein diet for 3 consecutive days per week, initiated after clinical EAE onset, increased serum corticosterone levels, reduced proinflammatory cytokines, and improved the clinical course of the disease. FMD also promoted oligodendrocyte differentiation and remyelination in the cuprizone-induced model of CNS demyelination (Choi et al., 2016).

Several studies have focused on potential beneficial effects of DR in MS patients. DR was demonstrated to be safe in an observational study conducted in 40 adult MS patients with mild disability who were followed for 6 mo after fasting during the Ramadan month (Saadatnia et al., 2009). Another study of >200 relapsing-remitting MS patients with mild disability reported that Ramadan fasting improved mean physical and mental health composites of quality of life (Etemadifar et al., 2016).

In an 8-wk randomized feeding study, DR (22% daily calorie reduction) and intermittent DR (75% caloric reduction 2 d/wk) were each compared with a control diet and found to be safe and feasible in people with MS. DR of either type improved mood, as indicated by the Functional Assessment of MS Emotional Well-being subcomponent, while not altering fatigue or sleep quality

(Fitzgerald et al., 2018). A study enrolling 60 relapsing-remitting MS patients revealed that 1 wk of FMD followed by 6 mo of Mediterranean diet or ketogenic diet improved some quality of life measures (Choi et al., 2016).

Our group performed a randomized trial of 15 d of intermittent DR versus normal diet in 16 MS patients being treated with corticosteroids for acute MS relapse. IF was well tolerated and reduced leptin without altering adiponectin levels. Enrichment of specific gut bacteria similar to that observed in EAE mice undergoing IF was seen (Cignarella et al., 2018). We are currently performing a 12-wk randomized controlled pilot study of intermittent DR (2 d/wk) compared with a Western diet in 40 MS patients (NCT03539094) to investigate its effects on peripheral blood inflammatory markers and gut microbiota. Also currently underway is an 18-mo, three-arm study in 111 relapsing MS patients comparing ketogenic diet versus IF (1 wk of fasting every 6 mo, plus fasting  $\geq 14$  h per day) versus a vegetarian-focused diet, and with new MRI lesions as the primary outcome measure (NCT03508414).

### Conclusions and future directions

Neurodegenerative diseases, among many other chronic conditions, are on the rise. The epidemic of obesity and unhealthy aging that is rapidly spreading from industrialized to developing countries likely has a role in this. Excessive calorie intake coupled with a sedentary lifestyle are major players in this extremely costly, and soon unsustainable, pandemic of unhealthy lifestyle-driven chronic diseases. People are living longer, but not healthier. More than 65% of people >65 yr old have two or more chronic diseases, such as heart disease, stroke, vascular dementia, type 2 diabetes, fatty liver disease, cancer, and kidney disease (Atella et al., 2019; Hung et al., 2011), which often share a common metabolic and molecular substrate (Fontana, 2018). As we have illustrated in this review, accumulating data suggest that targeting well-characterized nutrient-sensing and inflammatory pathways can reduce the accumulation of cellular and tissue damage and influence the clinical progression of neurological diseases such as PD, AD, and MS. Specific dietary manipulations play a significant role in modulating pathophysiological mechanisms leading to metabolic and inflammatory changes that characterize several neurodegenerative disorders (Fig. 2). For example, recent findings indicate that altering meal timing can improve brain energy metabolism and function in the absence of changes in overall energy intake. Lowered consumption of particular nutrients is also key in mediating some of the effects of DR, with protein and specific amino acids and nutritional modulation of the gut microbiome playing prominent roles (Fontana and Partridge, 2015). For example ketogenic diets can alter neuronal metabolic and electrical activities and are a proven effective treatment for children with drug-resistant epilepsy (Neal et al., 2008).

Based on our current knowledge, mechanism-based research on interventions to change diet, exercise, and other lifestyle patterns may be a safe and effective solution to slow brain aging and multiple neurodegenerative diseases before the onset of clinical symptoms (Cunnane et al., 2020). We base this comment on the reports that peripheral and central insulin resistance,

systemic inflammation, and disruption of brain energy metabolism are linked to the pathological processes of microglia activation, neurotoxic protein accumulation, axonal and synaptic dysfunction, and neuronal death observed in neurodegeneration (Aldana, 2019; Tups et al., 2017; Zilberter and Zilberter, 2017). As outlined in this review, DR and other dietary manipulations might be an effective approach to address metabolic and immune-inflammatory responses associated with impaired brain metabolism. Several clinical trials are underway to test the effects, efficacy, and safety of intermittent or chronic DR in subjects with AD or MS. The results of these trials will be extremely helpful to elucidate the importance of specific dietary manipulations and their potential side effects and risks, such as the potential long-term consequences of mild DR-induced hypercortisolism on learning and memory (Qiu et al., 2012), as well as other DR side effects (e.g., on bone mass and sex hormones), which will depend on the level of restriction (Most et al., 2017). However, more animal and human studies are warranted to understand the interactions among energy expenditure and calorie intake, meal frequency and timing, diet quality, and other factors such as the gut microbiome in slowing molecular damage leading to brain aging and CNS neurodegenerative diseases. Finally, an important practical consideration in choosing different approaches for DR is also its feasibility for the individual. Various types of intermittent DR (e.g., 5:2 diet or time-restricted feeding) are relatively easy ways to incorporate DR into the daily routine compared with chronic calorie restriction. Thus, continued investigation of the intersection of nutrition, metabolism, and neuroinflammation holds immense promise to prevent and potentially treat several chronic neurodegenerative diseases.

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