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Metabolic correction of neurodegenerative pathologies: the role of macronutrients and timing

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Abstract

Despite decades of intensive research, effective treatment and prevention strategies for neurodegenerative diseases (NDDs) remain elusive. This review focuses on Alzheimer's and Parkinson's diseases and acquired epilepsy suggesting that in their early phase, these progressive pathologies share common or interacting molecular pathways. Indeed, oxidative stress associated with disrupted glucose metabolism is the expected end state of most, if not all, risk factors preceding the onset of major NDDs. This review proposes that the initial oxidative stress in the brain resulting specifically from the hyperactivation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) causes a decline in glucose utilization and is the primary initiating factor of major NDDs. The existing clinical and experimental evidence points to NOX as the primary initiating mechanism shared within the major NDDs. During early oxidative stress, NOX activation is triggered in variable brain cells via multiple pathways, from beta-amyloid to alpha-synuclein, fibrin to glutamate and seizures. Therefore, the treatment strategy should have targeted the activation of NOX, wouldn't there be a lack of clinically approved selective NOX antagonists? On the other hand, there are promising metabolism-altering approaches via dietary means able to switch energy intake from glucose to ketones, which influences both oxidative stress and glucose utilization and could ameliorate disease progression. The regimen of time-restricted eating appears to be the most feasible, nutritious, and palatable one providing the essential benefits of a ketogenic diet without adverse effects.

Keywords

Glucose metabolism, ketogenic diet, Alzheimer's disease, beta-amyloid, Parkinson's disease, oxidative stress, nicotinamide adenine dinucleotide phosphate oxidase, acquired epilepsy

Neurodegenerative diseases

Neurodegenerative diseases (NDDs) represent the exceptional therapeutic challenge of our time. Despite decades of intensive research, effective treatment and prevention strategies remain elusive. Understanding

the primary initiating factors of sporadic NDDs is crucial in searching for a cure. While major NDDs vary greatly in affected brain areas and etiology, they share one common characteristic: all are characterized by energy (glucose) hypometabolism and oxidative stress. Numerous clinical and animal model studies have shown brain hypometabolism associated with oxidative stress to be an early (in some cases, the earliest) biomarker for most NDDs [1–4]. It is precisely this pathological combination that is likely the main initiating cause of the subsequent disease-associated detrimental cascades, and stopping it could finally prove to be an effective preventative strategy. The critical question here is, what is the exact trigger and source of this early pathology? This review proposes that the initiating oxidative stress (iOS) in the brain resulting specifically from the hyperactivation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is the primary initiating factor of major NDDs [3, 5–7].

Risk factors for NDDs

The risk factors for most NDDs overlap and lead to oxidative stress and energy deficiency [8–10]. Analysis of the preceding disease determinants reveals that disrupted glucose metabolism associated with oxidative stress and neuroinflammation is the expected end state of most, if not all, risk factors before the NDDs initiation [3]. As the result of analogous risk factors [8], major sporadic NDDs reveal similar detrimental hallmarks in the early stages, suggesting that these pathologies share common pathways initially. It is reasonable to propose therefore that uncovering the primary cause of these abnormalities might give a clue to efficient disease prevention.

Glucose hypometabolism

Normally, glucose is the primary fuel source in brain cells and the major substrate for endogenous antioxidant defense systems [11]. The underlying cause of glucose hypometabolism has been unclear until recently. Accumulating evidence renders oxidative stress a primary reason for glycolysis inhibition. Indeed, oxidative stress, which is defined as an imbalance between the cellular production of reactive oxygen species (ROS) and the cellular antioxidant system's ability to neutralize them readily, may cause deleterious modifications as it can change DNA structure, resulting in modification of proteins and lipids, activation of several stress-induced transcription factors, and production of proinflammatory and anti-inflammatory cytokines [12–14]. In particular, it is known that ROS can suppress glycolysis by inhibiting multiple glycolytic enzymes, including pyruvate kinase, phosphofructokinase, and glyceraldehyde-3-phosphate dehydrogenase [15–17]. Notably, methylglyoxal is a component of glycolytic reactions [18, 19] and may be cytotoxic due to its ability to generate advanced glycation end products (AGEs) which increase oxidative stress and have been implicated in stroke, diabetes, and NDDs such as Parkinson's disease (PD) and Alzheimer's disease (AD) [20–25].

Oxidative stress associated with deficient glucose metabolism may trigger acquired epilepsy, sporadic AD and PD [3]. Butterfield and Halliwell [16] presumed that beta-amyloid 42 ($A\beta_{42}$) oligomer-induced oxidative stress impairs glucose metabolism ultimately causing mild cognitive impairment (MCI) and AD. Our animal experiments showed that: 1) exogenous hydrogen peroxide (H_2O_2) inhibits glucose consumption [26]; 2) oxidative stress triggers seizures, while its prevention results in attenuation of epileptiform activity *in vivo* [27]; 3) $A\beta_{1\text{-}42}$-induced oxidative stress causes brain glucose hypometabolism and network dysfunction [7].

ROS overproduction

Strong experimental evidence indicates a significant role of oxidative stress in the initiation of glucose hypometabolism. The essential question is the origin of this oxidative stress. Indeed, if ROS overproduction is due to mitochondrial dysfunction, as often postulated in the literature, prevention of ROS generation would be highly problematic. At least 11 sites of ROS production have been identified in mitochondria [28, 29]. Though it was reasonably proposed that oxidative damage in neurodegeneration should be prevented via the direct inhibition of ROS production from specific sources, rather than via scavengers [30], such a goal in mitochondria is very tough to reach. In support of this notion, mitochondrially targeted antioxidants failed in clinical trials [1, 30–37]. We also demonstrated in brain slices that potent exogenous antioxidants failed

to impede fast ROS release during network activity [26]. Notwithstanding, accumulating evidence indicates the major role of NOX activity in iOS during NDD onset.

Mitochondrial dysfunction

It is very important to identify the principal source of oxidative stress in the onset of disease and find out whether mitochondrial dysfunction parallels the decrease in glucose consumption, or whether the glycolysis impairment induced by some specific source of oxidative stress precedes mitochondrial dysfunction. It is generally accepted that under physiological conditions mitochondria are the major source of ROS production (up to 90%) in the brain cells [38, 39], which imposed the conclusion of mitochondria-biased oxidative stress in many reports. However, although the brain is presumed to have a weak antioxidant defense [36, 40–42], this conclusion is not valid for mitochondria which possess a highly efficient system for antioxidant defense (consisting of several detoxifying enzymes such as glutathione, catalase, and others) [43–45], which normally neutralizes ROS as soon as they are generated. ROS are produced at various sites in mitochondria. Still, most of them are generated as by-products [superoxide anion (O_2^-)] of the electron transport chain during the oxidative phosphorylation process following the dismutation of O_2^- to H_2O_2 by copper and zinc superoxide dismutases in the intermembrane space and manganese superoxide dismutase in the matrix [30, 46, 47]. H_2O_2 removal can be two to three times faster than H_2O_2 production in rodent brain mitochondria [44, 45]. Therefore, the physiological emission of ROS from mitochondria is negligible considering oxidative stress [44], while may implement a signaling function [48, 49]. Moreover, due to its powerful scavenging potentials, mitochondria can neutralize penetrating cytoplasmic ROS and serve as their sink [28, 38, 44].

During pathology onset, deteriorated glycolysis would eventually lead to mitochondrial impairment, overproduction of ROS, and an increase in their emission to the cytoplasm in the subsequent stages of the disease, as has been shown in multiple studies [31, 34, 41, 50]. In addition, shifting the redox state balance towards oxidative stress may impair several mitochondrial proteins leading to dysfunction in the production of ATP and energy starvation [30, 47]. Indeed, it is generally accepted that the primary reason for mitochondrial dysfunction during NDDs is oxidative stress. It is highly unlikely, however, that the origin of such oxidative stress is mitochondria themself due to their potent antioxidant protection and high intrinsic resistance to oxidative stress [28, 51, 52]. More likely is the involvement of extra-mitochondrial ROS accumulation via the activity of other sources, e.g., NOX. This iOS may lead to damage/dysfunction of mitochondria, but its primary target would be cytoplasmic processes such as glycolysis.

Mitochondrial dysfunction occurs in all significant sporadic NDDs [53, 54], however, it is currently unknown whether oxidative mitochondrial damage occurs early in disease progression or is caused by secondary manifestations of the disease pathophysiology. Many authors agree that reduced energy metabolism and oxidative damage are at the center of NDD pathogenesis [1–4, 13, 55, 56]. Interestingly, although impaired glucose metabolism is one of the earliest features of the AD brain, the previous studies reported that early in AD, the cerebral metabolic rate of oxygen was not altered or was changed disproportionally to the prominent decrease in glucose utilization [57–59]. It was hypothesized that unaltered oxygen utilization and normal carbon dioxide (CO_2) production may indicate undisturbed substrate oxidation in mitochondria [57]. Moreover, other early studies that used the arterio-venous difference method showed that brain ketone uptake is still normal in moderately advanced AD [60, 61], while ketone catabolism is entirely mitochondrial. Recent studies using positron emission tomography (PET) ketone tracer, carbon-11-labeled acetoacetate (^{11}C-acetoacetate), reported that brain metabolism of ketones is unchanged in MCI and early AD [57, 62–66] supporting the previous assumption that oxidative phosphorylation may still be normal in the AD onset. This suggests that brain hypometabolism in prodromal AD may be specific to glucose and the primary site of metabolic abnormalities is glycolysis [63] but does not include dysfunctional mitochondrial oxidative phosphorylation. Indeed, it is highly problematic to explain the normal brain ketone metabolism unless suggesting that the enzymes of mitochondrial oxidative phosphorylation continue to function relatively normally, at least early in AD.

In animal experiments, mitochondria were reported not to be the main source of ROS overproduction in AD models [30, 52] and during seizure activity [67, 68]. We also did not observe the change in oxygen

consumption either during epileptiform network hyperactivity [26] or under the application of $A\beta_{1-42}$ [7, 69] suggesting maintained mitochondrial functioning, while a significant reduction in glucose utilization was detected in all cases.

Finally, supporting the proposition of minor mitochondria contribution to the iOS triggering major central nervous system diseases, mitochondrially targeted antioxidant therapies have been tested in clinical trials but failed to reveal evident benefits [1, 30–37].

Contribution of NOX to iOS

NOXs have been known for a long time to be responsible for the respiratory burst in phagocytes [70]. This unique enzyme family has the only biological function of ROS generation. The extensive expression of NOX isoforms has been discovered rather recently in a variety of brain cells [71] with NOX2 and NOX4 being the most prominent isoforms detected in neurons, microglia, and astrocytes [72, 73].

NOXs are multi-subunit enzymes, comprising membrane subunits and cytosolic subunits. Under the resting condition, NOX is normally dormant and the cytosolic components remain dispersed in the cytosol. Still, upon activation, which requires specific agonists, e.g., in neurons, NOX activation requires *N*-methyl-*D*-aspartate receptor stimulation [74], cytosolic components translocate to the membrane and assemble to the functioning complex [75]. Interestingly, NOX-generated ROS appeared as a major source of oxidative stress in NDDs, including AD, PD, and amyotrophic lateral sclerosis (ALS) [5, 76–78], as well as in acquired epilepsy and stroke [68, 79–81].

In animal experiments, we demonstrated that spontaneous seizure-like events in brain slices were initiated by NOX activation, while NOX inhibition prevented their generation [27]. Moreover, inhibition of NOX *in vivo* suppressed epileptiform activity in several seizure models [27]. In addition, $A\beta_{1-42}$ was found to be an agonist of NOX [5, 82, 83] and we demonstrated both in slices and *in vivo* that Aβ-NOX-induced oxidative stress resulted in prominent glucose hypometabolism [7, 84]. Importantly, recent studies suggested alpha-synuclein-induced activation of NOX [83]. Several recent reviews summarized current progress regarding the crucial role of NOX enzymes in NDDs like PD, AD, Huntington's disease, multiple sclerosis, and ALS, and in acute neurological disorders such as stroke, spinal cord injury, traumatic brain injury, and related cerebrovascular diseases [5, 73, 76, 83, 85].

How to counteract iOS induced by NOX in humans

The activated NOXs generate superoxide in phagocytes providing a major role in the human immune response [70]. This fact justifies the obvious conclusion that non-selective inhibition of NOXs is not a suitable option in developing NOX-targeting treatment. Therefore, only a selective inhibition of NOX family members may be considered to avoid harmful side effects. Targeting NOX activity without any off-target effects was recently impossible because of the lack of isoform-specific inhibitors. About thirty NOX inhibitors have been analyzed in recent comprehensive reviews [6, 86, 87], but only a few selective antagonists have been synthesized, specifically for NOX2 and NOX4 isoforms, at present, and only one (GKT137831, a specific inhibitor of NOX1 and NOX4) is in human clinical trials (phase 2) for pulmonary fibrosis and cirrhosis [6]. Several other promising inhibitors have been recently developed, such as NOS31 for NOX1, CPP11G/CPP11H and GSK2795039 for NOX2, and GLX7013114 for NOX4. Altogether, as NOX isoforms are well identified and studied, the elaboration of efficient selective inhibitors is hopefully a question of the nearest future.

Perspective

Therefore, the disorders mentioned above differ markedly in their etiology but they share common pathologies in brain function—oxidative stress and glucose hypometabolism, which principally define the disease onset and pathogenesis. This knowledge provides a potential opportunity to elaborate on a treatment counteracting oxidative stress and glucose hypometabolism and thus be efficient in curing/preventing the diseases. Unfortunately, at present, there is a lack of clinically available pharmaceuticals able to counteract the disease-initiating pathologies. On the other hand, lifestyle interventions have emerged in the spotlight and an increasing body of evidence suggests that dietary means can influence pathophysiological

features of NDDs and therefore could alter the course of disease neurological conditions. To tackle this problem, various nutrition interventions have been suggested including dietary supplements and dietary restrictions. Former regiments supposed the intake of specific nutrients, while the latter restricted particular nutrient(s) (e.g., carbohydrates) or time-restricted eating patterns, which can result in marked long-term changes in brain metabolism and functions such as neurogenesis and synaptic plasticity, oxidative stress and inflammation or epigenetic regulations as well as gut microbiota changes [9, 88–93].

Based on the assumption that the efficient diet has to counteract both brain oxidative stress and glucose hypometabolism, which presumably trigger the onset of NDDs, the only available strategy which satisfies these requirements is based upon a metabolic shifting from carbohydrates to fat utilization resulting in ketosis and a substantial increase of ketones level in the blood. The classical example of this approach is the ketogenic diet (KD), the only widely clinically accepted metabolic treatment for epilepsy [94]. The KD provides an alternative fuel substrate for mitochondria and thus supports brain energy production especially when glucose metabolism is impaired as in the case of NDDs. The clinical KD incorporates a 4:1 ratio of fat to protein plus carbohydrate that results in an increase in ketone blood level from < 100 μmol/L (typically observed in diets with unrestricted carbohydrate utilization) up to > 3 mmol/L [95]. In the brain, ketones bypass the glycolytic pathway directly entering mitochondria, thus constituting an even more efficient energy source than glucose and promoting mitochondrial oxidative metabolism [96–98]. Importantly, as mentioned above, the brain mitochondrial metabolism of ketones is unchanged in the prodromal stage of AD [57, 62–66] despite significantly impaired glucose utilization, indicating that ketones are able indeed to substitute glucose in energy production at least early in the disease. In addition, to avoid oxidative stress, brain cells possess a cytoplasmic antioxidant system utilizing the glucose pentose-phosphate-pathway [99] where enzymes of the glutathione system are used for the neutralization of H_2O_2 [99–101]. The cellular redox state is also controlled by specific gene transcription factors [e.g., nuclear factor erythroid 2-related factor 2 (Nrf2)] which regulate more than 200 genes including those containing an antioxidant response element (ARE) in their promoter and activation of the Nrf2-ARE signaling enhances the expression of enzymes involved in antioxidant defense in pentose-phosphate-pathway [102]. However, during acute oxidative stress, the glutathione system activation occurs in seconds while the onset of transcriptional responses takes hours [99, 103]. The pentose-phosphate-pathway has a large reserve capacity for upregulation and when amplified by oxidative stress it may reach up to 30% of glucose utilization compared to 3–7% in physiological conditions [99, 100, 103]. Therefore, the efficiency of this cytoplasmic antioxidant system depends directly on glucose availability and the glucose-sparing effect of the KD may be crucial for the operation of cellular antioxidant defense during NDDs [11, 84]. Moreover, it has been reported that KD induces initially mild oxidative stress and is related to the systemic activation of the Nrf2 pathway [95, 104].

The clinical KD settings are presumably the most efficient, however, due to severe nutrition restrictions, the diet possesses long-term adverse effects such as uric acidemia, hypocitraturia, hypercalciuria, aciduria, decreased bone mineral density, anemia, neuropathy, and also includes frequent gastrointestinal disturbances such as constipation, abdominal pain, emesis, and gastroesophageal reflux disease [98]. In addition, clinical studies show that maintaining the KD can be challenging for adult patients due to poor tolerance and lack of motivation [92]. Therefore, a reasonable diet for adults has to integrate the main benefits of the KD but be free of its disturbing pitfalls.

It is worth mentioning a popular dietary regimen, caloric restriction, which reduces food intake without incurring malnutrition. In fact, both the KD and caloric restriction diets are thought to act primarily through the same mechanisms as both diets result in an overall reduction in caloric intake and an increased level of circulating ketone bodies [93, 105, 106]. Indeed, the caloric restriction regimen represents a specific case of intermittent fasting, which is discussed below. Moreover, the diet characteristics largely intertwine, e.g., intermittent fasting results in intermittent ketosis, known for its appetite suppression, which results in turn in voluntary calorie reduction. Meanwhile, intermittent fasting has more metabolic benefits than permanent calorie-restriction [93, 106].

Fasting: the first known treatment of neurological diseases

The ability to survive the seasonal and diurnal periods of fasting is evolutionarily acquired and thus is supported by appropriate homeostatic mechanisms. As a result, an altered metabolic state occurs—ketosis. Fasting as a treatment for epilepsy was first reported in 1910 [107]. In both animals and humans, fasting prevents and treats metabolic syndrome, a major risk factor for many neurological diseases. Fasting improves cognition, stalls age-related cognitive decline, slows neurodegeneration, reduces brain damage, enhances recovery after stroke, and mitigates the pathological and clinical features of epilepsy and multiple sclerosis in animal models [108]. The KD appeared as a metabolic imitation of fasting [109] (which was considered hard to implement) since both conditions induce ketosis [92]. However, adherence to the KD has also often been reported as difficult with noticeable side effects [98].

The neuro- and metabo-protective effects of ketogenic regimens are of great practical importance given the epidemics of metabolic and NDDs, particularly, in protecting the brain from hypometabolism [9, 110, 111]. On the other hand, there is recent evidence of a number of exclusive functions of glucose that must be kept in mind in the regiments seriously restricting carbohydrate content: the synthesis of glycogen and nucleotides, antioxidant protection, rapid generation of ATP, and the production of pyruvate [11].

Long-term fasting (from many days to weeks) is hard to implement and is not free of severe adverse effects [110]. A convenient form of the fast regimen, intermittent fasting, includes eating patterns in which individuals follow recurrently the prolonged time periods (16–48 h) with no food intake, while normal food intake between these periods. Intermittent fasting evokes evolutionarily conserved, adaptive cellular responses that are integrated into the body in a manner that improves glucose management, increases stress resistance, and suppresses inflammation [106]. Several clinical trials are underway to test the effects, efficacy, and safety of intermittent fasting in patients with NDDs [112, 113]. Indeed, the neuroprotective effects of intermittent fasting observed in preclinical studies and clinical trials suggest that this regimen has broad-spectrum benefits for many health conditions and could represent a promising treatment option, especially in the earliest stages of the disease [106, 114].

As mentioned above, in the fed state in humans, the blood levels of ketone bodies are low but rise within 8–12 h after the onset of fasting, reaching levels above 2 mmol/L by 24 h [115, 116]. During the intermittent fasting regimen, repeated exposure to fasting periods prompts cells to the lasting adaptive stress responses resulting in increased antioxidant defense and down-regulation of inflammation [106]. Interestingly, following the administration of individuals with "ketogenic drinks" containing medium-chain triglycerides, the blood concentration of ketones increased rapidly but returned to the low basal level during a few hours [117, 118]. An analogous situation occurred at one-week intermittent fasting when blood ketone levels markedly increased during two fasting days but the next day returned back to the baseline [119]. In contrast, during the recurrent intermittent fasting procedure, the baseline ketone levels were significantly increased [120, 121] suggesting that fundamental adaptive metabolic systemic alterations occurred including ketone production in the liver. This is in support of the proposition reported previously [106] that "periodic flipping of the metabolic switch not only provides the ketones that are necessary to fuel cells during the fasting period but also elicits highly orchestrated systemic and cellular responses that carry over into the fed state to bolster mental and physical performance, as well as disease resistance".

Time-restricted eating is the most convenient protocol

Regimens of intermittent fasting include 16–48 h periods with no food intake repeatedly [122], however, it has been noted that some people are unable or unwilling to adhere to a scheme with infrequent but longer fasting periods [110, 123] and it is not recommended to AD and PD patients with a risk of malnutrition [111]. Therefore, a type of intermittent fasting, time-restricted eating (or feeding in animal experiments), which leads to the benefits of total fasting without obligatory reduction of nutrient intake appears to be the most convenient protocol [124].

In humans, the timing of meals is adjusted to the light-darkness cycle rather than to genetically determined metabolic cycles, thus the prolongation of the light phase due to artificial illumination makes the

calorie-restriction protocols challenging to comply with [125]. In experiments with free-running circadian rhythms in isolated environments, the sleep-wake cycle governed the meal timing, and the duration of both increased due to the exclusion of culturally determined [113, 126].

Time-restricted eating is a dietary regime that gathers all calorie intake independent from their macronutrient composition into 6–10 h during the active phase of the day [127]. Excluding the use of nutritional supplements, this is the only feasible way of compensation for nutritional deficiencies, unavoidable in any restrictive regime [127]. Intermittent ketosis protocol allows one balanced meal daily, complemented by 1–2 ketogenic meals [128]. Intermittent fasting protocols include alternate-day fasting and fasting for two days per week [129]. Time-restricted eating achieved by consistently reducing daily meal counts is more feasible than intermittent fasting. Time-restricted eating improves glucose control and insulin sensitivity and reduces oxidative stress [130–132]. It includes a direct antiepileptic calorie-restriction effect since it results in a voluntary reduction in energy intake and exerts long-term neuroprotective effects [124, 133].

There is an additional option to make the time-restricted eating regimen more feasible and palatable. Indeed, both chronic and periodic carbohydrate restriction in high-fat diets metabolically wise mimics fasting [134–140]. By the same token, a high-fat/low-carbohydrate breakfast mimics the metabolic features of time-restricted eating. Indeed, eating a very high-fat breakfast improved cognition [106, 141–144] supposedly by prolonging the overnight fast effects since Freemantle et al. [145] showed that a ketogenic breakfast does not interrupt overnight ketosis. Consequently, both the "ham and egg" ketogenic breakfast [146] and skipping breakfast results in a metabolic condition that can be termed intermittent ketosis. In terms of meal timing, skipping breakfast represents a type of intermittent fasting [138, 147, 148] leading to intermittent ketosis known for its appetite suppression effect [149] resulting in voluntary calorie reduction (e.g., [150]). Breakfast skipping and exclusion of late eating results in a reduction of voluntary calorie intake [151, 152], which is important since calorie-restriction has been shown to have profound metabolic benefits including neuroprotective, anti-ageing, and anti-inflammatory [110, 153]. Furthermore, Mattson et al. [154] suggested intermittent fasting has more metabolic benefits than permanent calorie-restriction. Thus, skipping breakfast may be more beneficial than traditional restrictive dieting.

Various supplementary nutrients (unsaturated fatty acids, complex sugars, fibers, etc.) positively affecting brain functions have been described in the literature (see e.g., [88, 91, 155]). We would like to mention pyruvate specifically since it's a unique array of neuroprotective properties and its ability to restore substantially glucose metabolism impaired by oxidative stress [26, 84, 156].

Conclusions

Fasting is the first known treatment of NDDs in history. The neurodegenerative processes trigger the four major pathologies: 1) oxidative stress; 2) hypometabolism of glucose leading to energy deficiency; 3) neuroinflammation; and 4) insulin resistance. Intermittent ketosis and its metabolic equivalents are efficient in preventing all of them excluding impaired glycolysis. Supplementation by oral pyruvate can be the missing part of the equation. Nowadays ketosis is considered a metabolic analogue of fasting [157, 158], it is well-known that the ketogenic regimen can reproduce the effects of fasting, and that ketogenic meals mimic the fasting period in time-restricted protocols. On the other hand, both chronic and periodic carbohydrate restrictions also produce effects characteristic of fasting. This unifying phenomenon can be termed "guided metabolic timing". It can include skipping and eating ketogenic breakfast since they both result in intermittent ketosis. These regiments cause a reduction of voluntary calorie intake thus they are metabolically favorable. Thus, pyruvate and intermittent ketosis combined might counteract all four major neurodegenerative pathologies and provide a core for efficient disease treatment.

Abbreviations

AD: Alzheimer's disease

$A\beta_{42}$: beta-amyloid 42

H_2O_2: hydrogen peroxide

iOS: initiating oxidative stress

KD: ketogenic diet

NDDs: neurodegenerative diseases

NOX: nicotinamide adenine dinucleotide phosphate oxidase

Nrf2: nuclear factor erythroid 2-related factor 2

PD: Parkinson's disease

ROS: reactive oxygen species

Declarations

Author contributions

YZ and TZ: Conceptualization, Formal analysis, Visualization, Writing—original draft, Writing—review & editing. Both of the authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

1. Liu Z, Zhou T, Ziegler AC, Dimitrion P, Zuo L. Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. Oxid Med Cell Longev. 2017;2017:2525967.
2. Tang BL. Glucose, glycolysis, and neurodegenerative diseases. J Cell Physiol. 2020;235:7653–62.
3. Zilberter Y, Zilberter M. The vicious circle of hypometabolism in neurodegenerative diseases: ways and mechanisms of metabolic correction. J Neurosci Res. 2017;95:2217–35.
4. Butterfield DA, Favia M, Spera I, Campanella A, Lanza M, Castegna A. Metabolic features of brain function with relevance to clinical features of Alzheimer and Parkinson diseases. Molecules. 2022;27:951.
5. Tarafdar A, Pula G. The role of NADPH oxidases and oxidative stress in neurodegenerative disorders. Int J Mol Sci. 2018;19:3824.
6. Begum R, Thota S, Abdulkadir A, Kaur G, Bagam P, Batra S. NADPH oxidase family proteins: signaling dynamics to disease management. Cell Mol Immunol. 2022;19:660–86.
7. Malkov A, Popova I, Ivanov A, Jang SS, Yoon SY, Osypov A, et al. Aβ initiates brain hypometabolism,

network dysfunction and behavioral abnormalities via NOX2-induced oxidative stress in mice. Commun Biol. 2021;4:1054.

8. Armstrong R. What causes neurodegenerative disease? Folia Neuropathol. 2020;58:93–112.
9. Kim CK, Sachdev PS, Braidy N. Recent neurotherapeutic strategies to promote healthy brain aging: are we there yet? Aging Dis. 2022;13:175–214.
10. Avitan I, Halperin Y, Saha T, Bloch N, Atrahimovich D, Polis B, et al. Towards a consensus on Alzheimer's disease comorbidity? J Clin Med. 2021;10:4360.
11. Zilberter Y, Zilberter T. Glucose-sparing action of ketones boosts functions exclusive to glucose in the brain. eNeuro. 2020;7:ENEURO.0303-20.2020.
12. Checa J, Aran JM. Reactive oxygen species: drivers of physiological and pathological processes. J Inflamm Res. 2020;13:1057–73.
13. Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladâcenco O, Roza E, et al. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. Int J Mol Sci. 2022;23:5938.
14. Bai R, Guo J, Ye XY, Xie Y, Xie T. Oxidative stress: the core pathogenesis and mechanism of Alzheimer's disease. Ageing Res Rev. 2022;77:101619.
15. Butterfield DA, Hardas SS, Lange ML. Oxidatively modified glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Alzheimer's disease: many pathways to neurodegeneration. J Alzheimers Dis. 2010;20:369–93.
16. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019;20:148–60.
17. Mullarky E, Cantley LC. Diverting glycolysis to combat oxidative stress. In: Nakao K, Minato N, Uemoto S, editors. Innovative medicine: basic research and development. Tokyo: Springer; 2015. pp. 3–23.
18. Chakraborty S, Karmakar K, Chakravortty D. Cells producing their own nemesis: understanding methylglyoxal metabolism. IUBMB Life. 2014;66:667–78.
19. Kalapos MP. Methylglyoxal in living organisms: chemistry, biochemistry, toxicology and biological implications. Toxicol Lett. 1999;110:145–75.
20. Zhang S, Lachance BB, Mattson MP, Jia X. Glucose metabolic crosstalk and regulation in brain function and diseases. Prog Neurobiol. 2021;204:102089.
21. de Bari L, Scirè A, Minnelli C, Cianfruglia L, Kalapos MP, Armeni T. Interplay among oxidative stress, methylglyoxal pathway and S-glutathionylation. Antioxidants (Basel). 2020;10:19.
22. Cepas V, Collino M, Mayo JC, Sainz RM. Redox signaling and advanced glycation endproducts (AGEs) in diet-related diseases. Antioxidants (Basel). 2020;9:142.
23. D'Cunha NM, Sergi D, Lane MM, Naumovski N, Gamage E, Rajendran A, et al. The effects of dietary advanced glycation end-products on neurocognitive and mental disorders. Nutrients. 2022;14:2421.
24. Reddy VP, Aryal P, Darkwah EK. Advanced glycation end products in health and disease. Microorganisms. 2022;10:1848.
25. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song BJ. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Exp Mol Med. 2021;53:168–88.
26. Malkov A, Ivanov AI, Buldakova S, Waseem T, Popova I, Zilberter M, et al. Seizure-induced reduction in glucose utilization promotes brain hypometabolism during epileptogenesis. Neurobiol Dis. 2018;116:28–38.
27. Malkov A, Ivanov AI, Latyshkova A, Bregestovski P, Zilberter M, Zilberter Y. Activation of nicotinamide adenine dinucleotide phosphate oxidase is the primary trigger of epileptic seizures in rodent models. Ann Neurol. 2019;85:907–20.
28. Napolitano G, Fasciolo G, Venditti P. Mitochondrial management of reactive oxygen species. Antioxidants (Basel). 2021;10:1824.

29. Brand MD. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. Free Radic Biol Med. 2016;100:14–31.
30. Angelova PR, Abramov AY. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. FEBS Lett. 2018;592:692–702.
31. Wang Y, Xu E, Musich PR, Lin F. Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. CNS Neurosci Ther. 2019;25:816–24.
32. Kim GH, Kim JE, Rhie SJ, Yoon S. The role of oxidative stress in neurodegenerative diseases. Exp Neurobiol. 2015;24:325–40.
33. Ienco EC, LoGerfo A, Carlesi C, Orsucci D, Ricci G, Mancuso M, et al. Oxidative stress treatment for clinical trials in neurodegenerative diseases. J Alzheimers Dis. 2011;24:111–26.
34. Jurcau A. Insights into the pathogenesis of neurodegenerative diseases: focus on mitochondrial dysfunction and oxidative stress. Int J Mol Sci. 2021;22:11847.
35. Kumar A, Singh A. A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. Front Pharmacol. 2015;6:206.
36. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. Molecules. 2019;24:1583.
37. Perez Ortiz JM, Swerdlow RH. Mitochondrial dysfunction in Alzheimer's disease: role in pathogenesis and novel therapeutic opportunities. Br J Pharmacol. 2019;176:3489–507.
38. Andreyev AY, Kushnareva YE, Murphy AN, Starkov AA. Mitochondrial ROS metabolism: 10 years later. Biochemistry (Mosc). 2015;80:517–31.
39. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell. 2005;120:483–95.
40. Cobley JN, Fiorello ML, Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. Redox Biol. 2018;15:490–503.
41. Millichap LE, Damiani E, Tiano L, Hargreaves IP. Targetable pathways for alleviating mitochondrial dysfunction in neurodegeneration of metabolic and non-metabolic diseases. Int J Mol Sci. 2021;22:11444.
42. Patel M. Targeting oxidative stress in central nervous system disorders. Trends Pharmacol Sci. 2016;37:768–78.
43. Andreyev AY, Kushnareva YE, Starkov AA. Mitochondrial metabolism of reactive oxygen species. Biochemistry (Mosc). 2005;70:200–14.
44. Starkov AA. The role of mitochondria in reactive oxygen species metabolism and signaling. Ann N Y Acad Sci. 2008;1147:37–52.
45. Munro D, Pamenter ME. Comparative studies of mitochondrial reactive oxygen species in animal longevity: technical pitfalls and possibilities. Aging Cell. 2019;18:e13009.
46. Venditti P, Di Stefano L, Di Meo S. Mitochondrial metabolism of reactive oxygen species. Mitochondrion. 2013;13:71–82.
47. Tirichen H, Yaigoub H, Xu W, Wu C, Li R, Li Y. Mitochondrial reactive oxygen species and their contribution in chronic kidney disease progression through oxidative stress. Front Physiol. 2021;12:627837.
48. Andreyev AY, Kushnareva YE, Starkova NN, Starkov AA. Metabolic ROS signaling: to immunity and beyond. Biochemistry (Mosc). 2020;85:1650–67.
49. Zarse K, Ristow M. Mitochondrial ROS signals prevent excessive immune response. Nat Metab. 2021;3:588–9.
50. Onyango IG, Bennett JP, Stokin GB. Regulation of neuronal bioenergetics as a therapeutic strategy in neurodegenerative diseases. Neural Regen Res. 2021;16:1467–82.
51. Zhang B, Pan C, Feng C, Yan C, Yu Y, Chen Z, et al. Role of mitochondrial reactive oxygen species in homeostasis regulation. Redox Rep. 2022;27:45–52.
52. Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev.

2012;2012:428010.

53. Federico A, Cardaioli E, Da Pozzo P, Formichi P, Gallus GN, Radi E. Mitochondria, oxidative stress and neurodegeneration. J Neurol Sci. 2012;322:254–62.
54. Ozgen S, Krigman J, Zhang R, Sun N. Significance of mitochondrial activity in neurogenesis and neurodegenerative diseases. Neural Regen Res. 2022;17:741–7.
55. Chen Z, Yuan Z, Yang S, Zhu Y, Xue M, Zhang J, et al. Brain energy metabolism: astrocytes in neurodegenerative diseases. CNS Neurosci Ther. 2023;29:24–36.
56. Zhou Y, Zhen Y, Wang G, Liu B. Deconvoluting the complexity of reactive oxygen species (ROS) in neurodegenerative diseases. Front Neuroanat. 2022;16:910427.
57. Hoyer S, Oesterreich K, Wagner O. Glucose metabolism as the site of the primary abnormality in early-onset dementia of Alzheimer type? J Neurol. 1988;235:143–8.
58. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol. 2004;490:115–25.
59. Hoyer S. Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. Mol Chem Neuropathol. 1992;16:207–24.
60. Lying-Tunell U, Lindblad BS, Malmlund HO, Persson B. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. Acta Neurol Scand. 1981;63:337–50.
61. Ogawa M, Fukuyama H, Ouchi Y, Yamauchi H, Kimura J. Altered energy metabolism in Alzheimer's disease. J Neurol Sci. 1996;139:78–82.
62. Cunnane SC, Trushina E, Morland C, Prigione A, Casadesus G, Andrews ZB, et al. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nat Rev Drug Discov. 2020;19:609–33.
63. Cunnane SC, Courchesne-Loyer A, Vandenberghe C, St-Pierre V, Fortier M, Hennebelle M, et al. Can ketones help rescue brain fuel supply in later life? Implications for cognitive health during aging and the treatment of Alzheimer's Disease. Front Mol Neurosci. 2016;9:53.
64. Croteau E, Castellano CA, Fortier M, Bocti C, Fulop T, Paquet N, et al. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. Exp Gerontol. 2018;107:18–26.
65. Castellano CA, Nugent S, Paquet N, Tremblay S, Bocti C, Lacombe G, et al. Lower brain ^{18}F-fluorodeoxyglucose uptake but normal ^{11}C-acetoacetate metabolism in mild Alzheimer's disease dementia. J Alzheimers Dis. 2015;43:1343–53.
66. Kapogiannis D, Avgerinos KI. Chapter three - Brain glucose and ketone utilization in brain aging and neurodegenerative diseases. In: Söderbom G, Esterline R, Oscarsson J, Mattson MP, editors. International Review of Neurobiology. Academic Press; 2020. pp. 79–110.
67. Shekh-Ahmad T, Kovac S, Abramov AY, Walker MC. Reactive oxygen species in status epilepticus. Epilepsy Behav. 2019;101:106410.
68. Kovac S, Dinkova Kostova AT, Herrmann AM, Melzer N, Meuth SG, Gorji A. Metabolic and homeostatic changes in seizures and acquired epilepsy—mitochondria, calcium dynamics and reactive oxygen species. Int J Mol Sci. 2017;18:1935.
69. Zilberter M, Ivanov A, Ziyatdinova S, Mukhtarov M, Malkov A, Alpár A, et al. Dietary energy substrates reverse early neuronal hyperactivity in a mouse model of Alzheimer's disease. J Neurochem. 2013;125:157–71.
70. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev. 2007;87:245–313.
71. Sorce S, Krause KH. NOX enzymes in the central nervous system: from signaling to disease. Antioxid Redox Signal. 2009;11:2481–504.

72. Sorce S, Stocker R, Seredenina T, Holmdahl R, Aguzzi A, Chio A, et al. NADPH oxidases as drug targets and biomarkers in neurodegenerative diseases: what is the evidence? Free Radic Biol Med. 2017;112:387–96.
73. Hou L, Zhang L, Hong JS, Zhang D, Zhao J, Wang Q. Nicotinamide adenine dinucleotide phosphate oxidase and neurodegenerative diseases: mechanisms and therapy. Antioxid Redox Signal. 2020;33:374–93.
74. Minnella AM, Zhao JX, Jiang X, Jakobsen E, Lu F, Wu L, et al. Excitotoxic superoxide production and neuronal death require both ionotropic and non-ionotropic NMDA receptor signaling. Sci Rep. 2018;8:17522.
75. Rastogi R, Geng X, Li F, Ding Y. NOX activation by subunit interaction and underlying mechanisms in disease. Front Cell Neurosci. 2017;10:301.
76. Barua S, Kim JY, Yenari MA, Lee JE. The role of NOX inhibitors in neurodegenerative diseases. IBRO Rep. 2019;7:59–69.
77. Ma MW, Wang J, Zhang Q, Wang R, Dhandapani KM, Vadlamudi RK, et al. NADPH oxidase in brain injury and neurodegenerative disorders. Mol Neurodegener. 2017;12:7.
78. Waghela BN, Vaidya FU, Agrawal Y, Santra MK, Mishra V, Pathak C. Molecular insights of NADPH oxidases and its pathological consequences. Cell Biochem Funct. 2021;39:218–34.
79. Eastman CL, D'Ambrosio R, Ganesh T. Modulating neuroinflammation and oxidative stress to prevent epilepsy and improve outcomes after traumatic brain injury. Neuropharmacology. 2020;172:107907.
80. Lin TK, Chen SD, Lin KJ, Chuang YC. Seizure-induced oxidative stress in status epilepticus: is antioxidant beneficial? Antioxidants (Basel). 2020;9:1029.
81. Brennan-Minnella AM, Won SJ, Swanson RA. NADPH oxidase-2: linking glucose, acidosis, and excitotoxicity in stroke. Antioxid Redox Signal. 2015;22:161–74.
82. Shelat PB, Chalimoniuk M, Wang JH, Strosznajder JB, Lee JC, Sun AY, et al. Amyloid beta peptide and NMDA induce ROS from NADPH oxidase and AA release from cytosolic phospholipase A_2 in cortical neurons. J Neurochem. 2008;106:45–55.
83. Abramov AY, Potapova EV, Dremin VV, Dunaev AV. Interaction of oxidative stress and misfolded proteins in the mechanism of neurodegeneration. Life (Basel). 2020;10:101.
84. Zilberter Y, Popova I, Zilberter M. Unifying mechanism behind the onset of acquired epilepsy. Trends Pharmacol Sci. 2022;43:87–96.
85. Lee SH, Lee M, Ko DG, Choi BY, Suh SW. The role of NADPH oxidase in neuronal death and neurogenesis after acute neurological disorders. Antioxidants (Basel). 2021;10:739.
86. Augsburger F, Filippova A, Rasti D, Seredenina T, Lam M, Maghzal G, et al. Pharmacological characterization of the seven human NOX isoforms and their inhibitors. Redox Biol. 2019;26:101272.
87. Chocry M, Leloup L. The NADPH oxidase family and its inhibitors. Antioxid Redox Signal. 2020;33:332–53.
88. Milošević M, Arsić A, Cvetković Z, Vučić V. Memorable food: fighting age-related neurodegeneration by precision nutrition. Front Nutr. 2021;8:688086.
89. Duplantier SC, Gardner CD. A critical review of the study of neuroprotective diets to reduce cognitive decline. Nutrients. 2021;13:2264.
90. de Carvalho TS. Calorie restriction or dietary restriction: how far they can protect the brain against neurodegenerative diseases? Neural Regen Res. 2022;17:1640–4.
91. Carneiro L, Pellerin L. Nutritional impact on metabolic homeostasis and brain health. Front Neurosci. 2022;15:767405.
92. Pietrzak D, Kasperek K, Rękawek P, Piątkowska-Chmiel I. The therapeutic role of ketogenic diet in neurological disorders. Nutrients. 2022;14:1952.
93. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci. 2018;19:81–94. Erratum in: Nat Rev Neurosci. 2020;21:445.
94. Levy R, Cooper P. Ketogenic diet for epilepsy. Cochrane Database Syst Rev. 2003:CD001903.

95. Taylor MK, Sullivan DK, Keller JE, Burns JM, Swerdlow RH. Potential for ketotherapies as amyloid-regulating treatment in individuals at risk for Alzheimer's disease. Front Neurosci. 2022;16:899612.
96. Elamin M, Ruskin DN, Sacchetti P, Masino SA. A unifying mechanism of ketogenic diet action: the multiple roles of nicotinamide adenine dinucleotide. Epilepsy Res. 2020;167:106469.
97. Bough KJ, Wetherington J, Hassel B, Pare JF, Gawryluk JW, Greene JG, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol. 2006;60:223–35.
98. Zhu H, Bi D, Zhang Y, Kong C, Du J, Wu X, et al. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. Signal Transduct Target Ther. 2022;7:11.
99. Cherkas A, Holota S, Mdzinarashvili T, Gabbianelli R, Zarkovic N. Glucose as a major antioxidant: when, what for and why it fails? Antioxidants (Basel). 2020;9:140.
100. Dienel GA. Brain glucose metabolism: integration of energetics with function. Physiol Rev. 2019;99:949–1045.
101. Tang BL. Neuroprotection by glucose-6-phosphate dehydrogenase and the pentose phosphate pathway. J Cell Biochem. 2019;120:14285–95.
102. Saha S, Buttari B, Panieri E, Profumo E, Saso L. An overview of Nrf2 signaling pathway and its role in inflammation. Molecules. 2020;25:5474.
103. Stincone A, Prigione A, Cramer T, Wamelink MM, Campbell K, Cheung E, et al. The return of metabolism: biochemistry and physiology of the pentose phosphate pathway. Biol Rev Camb Philos Soc. 2015;90:927–63.
104. Milder JB, Liang LP, Patel M. Acute oxidative stress and systemic Nrf2 activation by the ketogenic diet. Neurobiol Dis. 2010;40:238–44.
105. Robbins JP, Solito E. Does neuroinflammation underlie the cognitive changes observed with dietary interventions? Front Neurosci. 2022;16:854050.
106. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med. 2019;381:2541–51. Erratum in: N Engl J Med. 2020;382:298. Erratum in: N Engl J Med. 2020;382:978.
107. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. West J Med. 1982;137:379–99.
108. Phillips MCL. Fasting as a therapy in neurological disease. Nutrients. 2019;11:2501.
109. Wilder RM. The effects of ketonemia on the course of epilepsy. Mayo Clin Proc. 1921;2:307–8.
110. Hofer SJ, Carmona-Gutierrez D, Mueller MI, Madeo F. The ups and downs of caloric restriction and fasting: from molecular effects to clinical application. EMBO Mol Med. 2022;14:e14418.
111. Włodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients. 2019;11:169.
112. Fontana L, Ghezzi L, Cross AH, Piccio L. Effects of dietary restriction on neuroinflammation in neurodegenerative diseases. J Exp Med. 2021;218:e20190086.
113. Gudden J, Arias Vasquez A, Bloemendaal M. The effects of intermittent fasting on brain and cognitive function. Nutrients. 2021;13:3166.
114. Brocchi A, Rebelos E, Dardano A, Mantuano M, Daniele G. Effects of intermittent fasting on brain metabolism. Nutrients. 2022;14:1275.
115. Cahill GF Jr. Fuel metabolism in starvation. Annu Rev Nutr. 2006;26:1–22.
116. Patel S, Alvarez-Guaita A, Melvin A, Rimmington D, Dattilo A, Miedzybrodzka EL, et al. GDF15 provides an endocrine signal of nutritional stress in mice and humans. Cell Metab. 2019;29:707–18.e8.
117. Fortier M, Castellano CA, St-Pierre V, Myette-Côté É, Langlois F, Roy M, et al. A ketogenic drink improves cognition in mild cognitive impairment: results of a 6-month RCT. Alzheimers Dement. 2021;17:543–52.
118. Stubbs BJ, Cox PJ, Evans RD, Santer P, Miller JJ, Faull OK, et al. On the metabolism of exogenous ketones

in humans. Front Physiol. 2017;8:848.

119. Cerniuc C, Fischer T, Baumeister A, Bordewick-Dell U. Impact of intermittent fasting (5:2) on ketone body production in healthy female subjects. Ernährungs Umschau. 2019;66:2–9.
120. Sulaj A, Kopf S, von Rauchhaupt E, Kliemank E, Brune M, Kender Z, et al. Six-month periodic fasting in patients with type 2 diabetes and diabetic nephropathy: a proof-of-concept study. J Clin Endocrinol Metab. 2022;107:2167–81.
121. Ooi TC, Meramat A, Rajab NF, Shahar S, Ismail IS, Azam AA, et al. Intermittent fasting enhanced the cognitive function in older adults with mild cognitive impairment by inducing biochemical and metabolic changes: a 3-year progressive study. Nutrients. 2020;12:2644.
122. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science. 2018;362:770–5.
123. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 2017;39:46–58.
124. Currenti W, Godos J, Castellano S, Mogavero MP, Ferri R, Caraci F, et al. Time restricted feeding and mental health: a review of possible mechanisms on affective and cognitive disorders. Int J Food Sci Nutr. 2021;72:723–33.
125. Zilberter T, Paoli A. Editorial: metabolic shifting: nutrition, exercise, and timing. Front Nutr. 2020;7:592863.
126. Green J, Pollak CP, Smith GP. The effect of desynchronization on meal patterns of humans living in time isolation. Physiol Behav. 1987;39:203–9.
127. Napierkowski DB, Prado KB. Nutritional needs in the older adult, guidelines and prevention strategies to optimize health and avoid chronic disease. Geriatr Gerontol Aging. 2021;15:e0210027.
128. Napoleão A, Fernandes L, Miranda C, Marum AP. Effects of calorie restriction on health span and insulin resistance: classic calorie restriction diet *vs.* ketosis-inducing diet. Nutrients. 2021;13:1302.
129. Harris L, Hamilton S, Azevedo LB, Olajide J, De Brún C, Waller G, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. JBI Database System Rev Implement Rep. 2018;16:507–47.
130. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab. 2018;27:1212–21.e3.
131. Boyd P, O'Connor SG, Heckman-Stoddard BM, Sauter ER. Time-restricted feeding studies and possible human benefit. JNCI Cancer Spectr. 2022;6:pkac032.
132. Cienfuegos S, McStay M, Gabel K, Varady KA. Time restricted eating for the prevention of type 2 diabetes. J Physiol. 2022;600:1253–64.
133. Zilberter T, Zilberter Y. Ketogenic ratio determines metabolic effects of macronutrients and prevents interpretive bias. Front Nutr. 2018;5:75.
134. Acosta-Rodríguez VA, Rijo-Ferreira F, Green CB, Takahashi JS. Importance of circadian timing for aging and longevity. Nat Commun. 2021;12:2862.
135. Longo VD, Di Tano M, Mattson MP, Guidi N. Intermittent and periodic fasting, longevity and disease. Nat Aging. 2021;1:47–59.
136. Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, et al. Effects of 4- and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity. Cell Metab. 2020;32:366–78.e3.
137. Ludwig DS, Aronne LJ, Astrup A, de Cabo R, Cantley LC, Friedman MI, et al. The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. Am J Clin Nutr. 2021;114:1873–85.
138. Zilberter T, Zilberter EY. Breakfast and cognition: sixteen effects in nine populations, no single recipe. Front Hum Neurosci. 2013;7:631.

139. Barañano KW, Hartman AL. The ketogenic diet: uses in epilepsy and other neurologic illnesses. Curr Treat Options Neurol. 2008;10:410–9.
140. Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol. 2012;3:59.
141. Bush NC, Resuehr HES, Goree LL, Locher JL, Bray MS, Soleymani T, et al. A high-fat compared with a high-carbohydrate breakfast enhances 24-hour fat oxidation in older adults. J Nutr. 2018;148:220–6.
142. Makowski MS, Trockel MT, Menon NK, Wang H, Katznelson L, Shanafelt TD. Performance nutrition for physician trainees working overnight shifts: a randomized controlled trial. Acad Med. 2022;97:426–35.
143. Bhoumik S, Rizvi SI. Anti-aging effects of intermittent fasting: a potential alternative to calorie restriction? Biologia. 2021;76:2329–36.
144. Fischer K, Colombani PC, Langhans W, Wenk C. Cognitive performance and its relationship with postprandial metabolic changes after ingestion of different macronutrients in the morning. Br J Nutr. 2001;85:393–405.
145. Freemantle E, Vandal M, Tremblay Mercier J, Plourde M, Poirier J, Cunnane SC. Metabolic response to a ketogenic breakfast in the healthy elderly. J Nutr Health Aging. 2009;13:293–8.
146. Smith A, Kendrick A, Maben A, Salmon J. Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning. Appetite. 1994;22:39–55.
147. la Fleur SE, Ji H, Manalo SL, Friedman MI, Dallman MF. The hepatic vagus mediates fat-induced inhibition of diabetic hyperphagia. Diabetes. 2003;52:2321–30.
148. Horn CC, Ji H, Friedman MI. Etomoxir, a fatty acid oxidation inhibitor, increases food intake and reduces hepatic energy status in rats. Physiol Behav. 2004;81:157–62.
149. Scharrer E. Control of food intake by fatty acid oxidation and ketogenesis. Nutrition. 1999;15:704–14.
150. Dutton SB, Sawyer NT, Kalume F, Jumbo-Lucioni P, Borges K, Catterall WA, et al. Protective effect of the ketogenic diet in *Scn1a* mutant mice. Epilepsia. 2011;52:2050–6.
151. Levitsky DA, Pacanowski CR. Effect of skipping breakfast on subsequent energy intake. Physiol Behav. 2013;119:9–16.
152. Gonzalez JT, Veasey RC, Rumbold PL, Stevenson EJ. Breakfast and exercise contingently affect postprandial metabolism and energy balance in physically active males. Br J Nutr. 2013;110:721–32.
153. Willcox BJ, Willcox DC. Caloric restriction, caloric restriction mimetics, and healthy aging in Okinawa: controversies and clinical implications. Curr Opin Clin Nutr Metab Care. 2014;17:51–8.
154. Mattson MP, Duan W, Guo Z. Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms. J Neurochem. 2003;84:417–31.
155. Piemontese L, Brunetti L, Leuci R. Can foods influence the onset and progress of neurodegenerative diseases? Neural Regen Res. 2022;17:2443–4.
156. Zilberter Y, Gubkina O, Ivanov AI. A unique array of neuroprotective effects of pyruvate in neuropathology. Front Neurosci. 2015;9:17.
157. Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 2016;23:1048–59.
158. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab. 2015;22:86–99.