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THE NEUROPROTECTIVE PROPERTIES OF CALORIE RESTRICTION, THE KETOGENIC DIET, AND KETONE BODIES

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Abstract

The therapeutic potential of calorie restriction and the ketogenic diet have been repeatedly demonstrated in clinical settings and in various animal models of neurological disease. The underlying mechanisms involve an improvement in mitochondrial function, a decrease in the expression of apoptotic factors and an increase in the activity of neurotrophic factors. Clinical applications of ketogenic diets have been significantly hampered however by poor tolerability and potentially serious side-effects. Recent research aimed at identifying a mediator that can reproduce the neuroprotective effects of calorie restriction with less demanding changes to dietary intake suggests that ketone bodies might represent an appropriate candidate. Ketone bodies protect neurons against multiple types of neuronal injury and the underlying mechanisms are similar to those of calorie restriction and of the ketogenic diet. The present review describes the neuroprotective effects of calorie restriction, the ketogenic diet and ketone bodies and compare the molecular mechanisms of action of these interventions.

Keywords

calorie restriction; neuroprotection; ketone bodies; ketogenic diet; oxidative stress; mitochondria; brain

1. Introduction

The anticonvulsant properties of fasting have been recognized since antiquity, strongly suggesting that fasting, and more generally, calorie restriction probably represents the first effective treatment for epileptic seizures in medical history. In addition, more recent evidence suggests that the benefits of calorie restriction, elicited either by daily reduction of energy intake or by intermittent fasting, are not limited to epilepsy and might in fact include a generalized neuroprotective effect applicable to many acute and chronic neurological diseases. In view of the present obesity epidemic, however, the scientific and medical communities have realized that calorie restriction is often not a practical treatment option. Similarly, the ketogenic diet, a high-fat, low-carbohydrate diet designed to reproduce the effects of fasting, has been difficult to use in clinical settings despite proven efficacy. As a consequence, considerable effort has been invested to understand the mechanisms underlying the neuroprotective effects of calorie restriction (and potentially of the ketogenic diet) with the hope of developing alternative therapeutic options.

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The present article reviews findings supporting the neuroprotective effects of calorie restriction, summarizes the mechanisms activated by calorie restriction and describes a mediator that could possibly replicate the neuroprotective effects of calorie restriction. Specifically, we propose that ketone bodies mediate, at least in part, the neuroprotective effects of calorie restriction by showing that ketone bodies are equally neuroprotective and that calorie restriction and ketone bodies act on neural cells by similar mechanisms.

2. Calorie restriction and neurological disease

2.1 Human studies

Obesity is associated with an increased risk of dementia (Kivipelto et al. 2005). On imaging studies, decreased hippocampal volume and increased white matter hyperintensities, two radiological indicators of pathological brain aging, are more common in obese patients (Jagust et al. 2005). In contrast, in addition to the well-known effects of fasting on seizure frequency, low dietary energy intake is associated with decreased incidence of Alzheimer's and Parkinson's diseases (New York City cohort), and calorie restriction for 6 months improves biomarkers associated with longevity including reduced fasting insulin levels, body temperature and DNA damage (Luchsinger et al. 2002; Heilbronn et al. 2006). Calorie restriction might even reduce disease risk and increase lifespan in normal weight subjects (Johnson et al. 2006). Beneficial effects on mental health have been reported as well, with improved mood following calorie restriction of obese diabetic patients (Wing et al. 1991). To date however, clinical trials looking at the effects of calorie restrictions on brain aging and neurological disease have not been performed and all available information is derived exclusively from animal models.

2.2 Animal models

Calorie restriction prolongs the lifespan of yeast, roundworms, rodents and monkeys, even when initiated in midlife (Means et al. 1993; Mattson 2003; Bordone and Guarente 2005; Guarente and Picard 2005). Moreover, age-related deficits in learning and motor coordination are reduced by calorie restriction in rodents (Mattson et al. 2003, 2006). Rats placed on a hypocaloric diet from the age of 3 weeks and tested at 2 years of age performed significantly better than aged-matched controls fed *ad libitum* on both spatial (Morris Water Maze, spatial version of the 8-arm radial maze) and non-spatial (non-spatial version of the 8-arm radial maze) learning tasks (Pitsikas et al. 1990; Pitsikas and Alegri 1992). Calorie restricted middle-aged and aged mice exhibited similar improvements in learning tasks that also included active and passive avoidance learning (Ingram et al. 1987; Means et al,. 1993; Hashimoto and Watanabe 2005). In parallel, calorie restriction also prevented age-related deficits in hippocampal long-term potentiation, a cellular correlate of memory (Hori et al. 1992; Eckles-Smith et al. 2000; Okada et al. 2003).

In addition to effects on aging, calorie restriction appears beneficial in several models of neurological disease, most notably epilepsy. In EL mice, an idiopathic model of stimulus-induced epilepsy, the onset of seizures typically occurs in the first few months of life but was significantly delayed for several weeks by calorie restriction (Greene et al. 2001; Mantis et al, 2004). In a different model, calorie restriction elevated the threshold to seizures elicited by tail-vein infusion of pentylenetetrazole (Eagles et al. 2003). Consistently, rats on a calorie-restricted diet exhibited reduced excitability in the dentate gyrus, as evidenced by greater paired-pulse inhibition and increased threshold, latency and duration of electrographic seizures following maximal dentate gyrus activation by angular bundle stimulation (Bough et al. 2003). Finally, intermittent fasting prevented spatial learning deficits in rats exposed to excitotoxic injury (Bruce-Keller et al. 1999). Improved cognitive function correlated with decreased neuronal death in the hippocampus.

In animal models of Parkinson's disease, calorie restriction improved motor function and enhanced neuronal survival in the substantia nigra of mice and monkeys exposed to MPTP, a neurotoxin that is converted to MPP^+ in astrocytes; MPP^+ is then transported into dopaminergic neurons where it inhibits NADH dehydrogenase and increases reactive oxygen species formation at complex I of the mitochondrial respiratory chain (Duan and Mattson 1999; Maswood et al. 2004). A comparable, neuroprotective effect was reported in the striatum of mice treated with 3-nitroproprionic acid, a succinate dehydrogenase inhibitor that causes motor and histological defects similar to those of Huntington's disease (Bruce-Keller et al. 1999). Calorie restriction also attenuated amyloid deposition in monkeys and in transgenic mouse models of Alzheimer's disease (Patel et al. 2004; Wang et al. 2004 Qin et al. 2006a,b), ameliorated cognitive deficits in a mouse model of Alzheimer's disease (Halagappa et al., 2007) and reduced neuronal loss in neocortex, hippocampus and striatum of rats subjected to a 30 minute, cerebral four-vessel occlusion, a model of ischemic stroke (Marie et al. 1990). Similarly, feeding rats on alternate days decreased infarct size and improved motor function following middle cerebral artery occlusion for 1 hour (Yu and Mattson 1999).

Although calorie restriction appears to exert beneficial effects in most studies of aging and neurological disease, an absence of such clinical effects and complications have been reported. First, several studies failed to reveal any influence of calorie restriction on spatial learning in both rats and mice (Bellush et al. 1996; Markowska 1999; Hansalik 2006). One study in rats actually found a worsening of cognitive function despite increased longevity (Yanai et al. 2004). Interestingly, cognitive deficits improved with glucose administration. Second, APP transgenic mice became hypoglycemic and died prematurely (within 2 – 3 weeks) despite a decrease in amyloid deposition (Pedersen et al., 1999). Third, in mice expressing the G93A familial ALS mutation, age of onset of paralysis was not affected and the disease progressed at a faster rate (Pedersen and Mattson, 1999). Reasons behind these discordant findings are not readily apparent but some studies have suggested that genetic variance among species and among the different strains in a single species might influence responses to calorie restriction (Willott et al. 1995; Markowska and Savonenko 2002 Mockett et al. 2006). Additional research is required to identify the factors that determine responsiveness to calorie restriction.

3. Cellular and Molecular Mechanisms of Action of Calorie Restriction

Several mechanisms have been proposed to explain the neuroprotective effects of caloric restriction. These can be grouped into two general categories: 1) improved mitochondrial function, leading to decreased production of reactive oxygen species and increased energy output; 2) regulation of gene expression, resulting in decreased activity of pro-apoptotic factors and increased levels of neuroprotective factors such as neurotrophins. Current hypotheses are mostly based, however, on data from primitive organisms or non-neuronal mammalian tissue, and are surrounded by considerable variability. In particular, several mechanisms that increase longevity in response to calorie restriction have the opposite effect on neuronal survival and resistance to injury

Recent findings suggest that many of the beneficial effects of caloric restriction on the nervous system may result from the activation of adaptive cellular stress responses, in a process called hormesis (Calabrese et al., 2007; Mattson, 2008a, 2008b). The calorie restriction imposes a mild stress on cells which results in the activation of stress response pathways including those involving transcription factors such as CREB, Nrf-2 and NF-κB (Mattson and Cheng, 2006). The cellular stress may result from a combination of the direct consequences of reduced energy intake and an increase in the activity of neuronal circuits secondary to increased hunger. This proposed neuroprotective mechanism of action of caloric restriction is analogous to the beneficial effects of physical exercise on muscle and heart cells, wherein energy demand, and oxidative and ionic stress increase during the exercise, and activate adaptive stress responses

in the cells. Indeed, some of the same classes of adaptive stress response proteins have been shown to be upregulated in neurons in response to calorie restriction and in muscles in response to exercise including heat-shock protein, growth factors and energy-regulating enzymes (Mattson and Wan, 2005; Martin et al., 2006).

3.1 Antioxidant effects

Although reactive oxygen species can be produced by cytoplasmic oxygenases as a result of increased intracellular calcium concentrations, mitochondria are the major source of reactive oxygen species, particularly complex I in neuronal mitochondria (Turrens 2003; Hunt et al. 2006). The superoxide anion radical is normally produced in low concentrations during oxidative phosphorylation, but levels increase substantially following mitochondrial injury – for example, as a result of intracellular calcium overload caused by excitotoxic injury (Balaban et al., 2005; Nicholls 2004). Superoxide is subsequently converted to hydrogen peroxide, a source of hydroxyl radicals. The resultant oxidative damage to proteins, lipids and DNA leads to manifestations of neurological disease (Keller et al., 2005; Mariani et al., 2005; Moreira et al., 2006; Reddy, 2006). A significant proportion of the neurological deficits that occur following stroke, head trauma, anoxia or even in Alzheimer's disease can in fact be attributed to secondary injury caused by glutamate excitotoxicity and, consequently, intracellular calcium overload, mitochondrial dysfunction and oxidative stress (Calabrese et al. 2001; Bramlett and Dietrich 2004; Canevari et al. 2004).

Calorie restriction delays age-related oxidative damage to DNA, proteins and lipids as evidenced by decreased tissue concentrations of peroxidised lipids, protein carbonyls and damaged bases in nuclear and mitochondrial DNA (Merry 2004; Hunt et al. 2006). Several mechanisms have been proposed to explain antioxidant properties of calorie restriction. First, some studies suggested that calorie restriction enhanced antioxidant defenses, including superoxide dismutase, glutathione peroxidase and catalase (Gong et al. 1997; Sreekumar et al. 2002; Agarwal et al. 2005; Rankin et al. 2006), although others found no significant effects (Sohal et al. 1994; Deruisseau et al. 2006). Second, a decrease in the mitochondrial production of reactive oxygen species has been demonstrated, specifically at complex I of the respiratory chain (Sohal et al. 1994 Merry 2002; Lambert and Merry 2004; Gredilla and Barja 2005). Brain mitochondria isolated from aged, calorie-restricted rats produced significantly less hydrogen peroxide than those from controls fed *ad libidum* in the presence of pyruvate and malate but not in the presence of succinate, consistent with an effect of calorie restriction at complex I (Sanz et al. 2005). The same conclusion was reached in studies of liver and heart mitochondria (Gredilla et al. 2001; Lopez-Torres et al. 2002).

How does calorie restriction actually decrease mitochondrial production of reactive oxygen species? The answer is unclear but the mechanism may involve uncoupling proteins (UCP) which span the mitochondrial inner membrane and allow the leakage of protons from the inter-membrane space to the matrix, thereby dissociating the electrochemical gradient (proton motive force) from ATP generation. This uncoupling diminishes the mitochondrial membrane potential and decreases the production of reactive oxygen species (Harper et al. 2004; Andrews et al. 2005; Bevilacqua et al.. 2005; Krauss et al. 2005). Consistently, enhanced UCP activity has been associated with increased longevity and neuronal resistance to ischemic, toxic, traumatic and epileptic injury (Diano et al. 2006 Mattiason et al. 2003 Sullivan et al. 2003 Andrews et al. 2006; Conti et al. 2005, 2006; Liu et al. 2006).

3.2 Increased metabolic efficiency

Slowing of brain aging in calorie-restricted animals was originally believed to result from reduced metabolic activity and, hence, decreased production of reactive oxygen species, a natural byproduct of oxidative metabolism (Wolf 2006). Several studies revealed that calorie

restriction was associated with energy conservation (Gonzales-Pacheco et al. 1993; Santos-Pintos et al. 2001) and that mitochondria isolated from calorie-restricted animals produced less ATP than those from controls fed ad libitum, a finding compatible with increased UCP activity (Sreekumar et al. 2002; Drew et al. 2003). However, separate investigations in rodents have suggested that, when adjusted for body weight, metabolic rate does not decrease with calorie restriction (Masoro et al. 1982; McCarter et al. 1985; Masoro 1993). More importantly, calorie restriction prevents the age-related decline in oxidative metabolism in muscle (Hepple et al. 2005; Baker et al. 2006). These data are supported by recent studies indicating that, in contrast to isolated mitochondria, ATP synthesis in intact myocytes and *in vivo* does not decrease following calorie restriction (Lopez-Lluch et al. 2006; Zangarelli et al. 2006). Additional support is provided by the finding that, in yeast, oxidative metabolism increases with calorie restriction (Lin et al. 2002).

Although the effects of calorie restriction on ATP generation might appear to contradict those on uncoupling proteins, this discrepancy can be explained by the fact that calorie restriction also promotes mitochondrial biogenesis, thereby enhancing total metabolic output per cell while decreasing mitochondrial production of reactive oxygen species (Diano et al. 2003; Nisoli et al. 2005; Civitarese et al. 2007). The neuroprotective benefits of this increased metabolic efficiency have not been directly investigated but would be expected to increase neuronal resistance to injury given that mitochondrial damage and energy failure are central components of many neurological disorders (Green and Kroemer 2004 Patel 2004; Moro et al. 2005; Martin 2006; Onyango and Khan 2006).

3.3 Increased sirtuin activity

Sirtuins are a large and diverse family of enzymes that regulate gene expression. The first sirtuin, silent information regulator 2 (Sir2), was described in yeast. Sir2 is a class III histone deacetylase that uses the cofactor nicotinamide adenine dinucleotide (NAD^+) in a catalytic reaction that releases nicotinamide, a feedback inhibitor, and *O*-acetyl ADP ribose (Imai et al. 2000; Mamorstein 2004 Sauve et al. 2006). It has been reported that increased Sir2 activity lengthens life span, and that calorie restriction increases Sir2 levels and does not promote longevity in SIR2 knockouts (Kaeberlein et al. 1999; Lin et al. 2000, 2004; Tissenbaum and Guarente 2001; Rogina and Helfand 2004). Calorie restriction may activate Sir2 by increasing NAD^+ levels (a result of improved mitochondrial function) or by increasing the expression of PNC1, a nicotinaminidase that would alleviate nicotinamide-mediated inhibition (Anderson et al. 2002, 2003; Gallo et al. 2004). These findings only apply, however, to the active replication (mitotic) phase but not to the chronological (post-mitotic) phase of the yeast life span, even though calorie restriction extends both phases (Bitterman et al. 2003; Fabrizio and Longo 2003; Longo and Kennedy 2006).

Replicative life span is measured by the number of divisions a yeast cell undergoes before dying. Yeast cells actively replicate only when nutrients are abundant. In contrast, chronological life span indicates the amount of time yeast survive without dividing following nutrient deprivation. Yeast cells can actually remain viable for weeks (and possibly longer) in a hypometabolic state when nutrients are scarce. Therefore, to study chronological life span, yeast cells are typically incubated in a special synthetic medium that promotes a relatively high metabolism while restricting replication. Interestingly, SIR2 deletion does not affect longevity under these conditions. Moreover, if calories are severely restricted, for example by incubating yeast cells in water, SIR2 deletion actually prolongs life span (Fabrizio et al. 2005).

In mammals, calorie restriction increases the expression of Sirt1, the Sir2 mammalian ortholog, in various tissues, including brain. Resveratrol, a natural Sirt1 activator found in red wine, lengthens the life span of mice and prevents the age-related deterioration of their motor function (Cohen et al. 2004; Baur et al. 2006). Moreover, several lines of evidence suggest that Sirt1

activation is neuroprotective. Sirt1 decreased amyloid Aβ accumulation in brains of Tg2576 mice (a model of Alzheimer's disease) and aged Squirrel monkeys by enhancing α-secretase processing of the amyloid precursor protein (Qin et al. 2006a,b). Consistently, resveratrol decreased Aβ toxicity in neuroblastoma and PC12 cells (Jang and Surh 2003; Savaskan et al. 2003). Moreover, resveratrol reduced neuronal dysfunction and death in nematode and murine models of Huntington's disease. The neuroprotective effects of resveratrol in *C. elegans* were replicated by increased dosage of Sir2.1, the nematode Sir2 ortholog, and were blocked by the sirtuin inhibitors nicotinamide and sirtinol (Parker et al. 2005). Slowing of axonal degeneration following peripheral neuronal injury in mice carrying the Wallerian degeneration slow mutation (wld^S) was also attributed to increased Sirt1 activity (Araki et al. 2004). In contrast, Sirt1 deficiency and nicotinamide, a sirtuin inhibitor, prolonged the replicative life spans of mouse embryonic and human fibroblasts chronically exposed to sublethal oxidative stress (Chua et al. 2006 Lim et al. 2006). Increased Sirt1 activity did however prevent apoptosis of mouse embryonic and human fibroblasts against acute administration of hydrogen peroxide at higher doses and against acute DNA damage (Luo et al.2001; Chua et al. 2006). The reasons behind these seemingly contradictory effects of Sirt1 in fibroblasts have not been elucidated.

Several mechanisms have been proposed to explain the effects of Sirt1 on neuronal survival. Sirt1 exhibits broad deacetylase activity. Identified targets include: the tumor suppressor protein p53; the forkhead transcription factors (class O) FOXO; the DNA repair protein Ku70; the peroxisome proliferator-activated receptor gamma (PPARγ); and the nuclear factor NFκB (Mattson et al. 2003; Hisahara et al. 2005; Anekonda and Reddy 2006 Martin et al. 2006). Sirt1 represses p53-dependent apoptosis triggered by acute oxidative stress or DNA damage in fibroblasts and mesangial cells (Luo et al. 2001; Vaziri et al. 2001; Kume et al. 2006). To our knowledge, however, the importance of Sirt1-mediated p53 deacetylation has not been directly evaluated in neurons. Sirt1 also prevents FOXO3-mediated apoptosis. Mammalian FOXO factors regulate the transcription of various genes involved in resistance to stress, DNA repair and apoptosis (Furukawa-Hibi et al. 2005). In cerebellar granule cells, fibroblasts and embryonic stem cells, apoptosis triggered by FOXO3 acetylation in response to oxidative stress and DNA damage is inhibited by Sirt1 (Brunet et al. 2004; Motta et al. 2004). Sirt1 also inhibits apoptosis by deacetylating the DNA repair protein Ku70, causing it to sequester the proapoptotic factor Bax (Cohen et al. 2004).

Sirt1-mediated deacetylation of the nuclear receptor PPARγ was originally identified as a pathway to longevity by repressing adipocyte formation and fat storage (Picard et al. 2004; Guarente and Picard 2005). More recent evidence suggests, however, that PPARγ is neuroprotective (Bordet et al. 2006; Sundararajan et al. 2006). PPARγ agonists reduced neuronal death secondary to NMDA excitotoxicity (Zhao et al. 2006), infarct size following middle cerebral artery occlusion (Pereira et al. 2005, 2006; Shuimau et al. 2005; Sundararajan et al. 2005), Aβ deposition in the hippocampus and cerebral cortex of Alzheimer's disease mouse models (Heneka et al. 2005; Sastre et al. 2003, 2006) and dopaminergic cell loss in a Parkinson's disease model (Breidert et al. 2002). Furthermore, PPARγ agonists improved cognitive function in patients with Alzheimer's disease (Watson et al. 2005; Risner et al. 2006), improved motor function and delayed death in murine models of amyotrophic lateral sclerosis (Kiaei et al. 2005; Schutz et al. 2005), and reduced clinical severity in experimental allergic encephalomyelitis, a model of multiple sclerosis (Niino et al. 2001; Feinstein et al. 2002; Natarajan et al. 2003). PPARγ has also been shown to stimulate neural stem cell growth and differentiation (Wada et al. 2006).

The mechanism of action of PPARγ that has received the most attention is decreased expression of inflammatory factors (Daynes and Jones 2002). This anti-inflammatory effect involves NFκB inhibition (Poynter and Daynes 2001 Hu et al. 2005; Pereira et al. 2005). It should be noted, however, that Sirt1 also deacetylates NF-κB (Yeung et al. 2004). Therefore, NFκB

repression by Sirt1 might compensate for the concomitant inhibition of PPARγ. Unfortunately, it is not clear if this combination of changes results in an overall neuroprotective effect because NFκB activation promoted neuronal survival in several studies (Barger et al., 1995; Mattson et al., 1997; Maggirwar et al. 1998; Hamanoue et al. 1999; Middleton et al. 2000; Fernyhough et al. 2005). Adding to the apparently contradictory effects mentioned above, Sirt1 was recently found to repress UCP2 in pancreatic beta cells, an unexpected finding given that calorie restriction upregulates UCP2 (Bordone et al. 2006). Moreover, several studies in yeast have recently questioned the role of sirtuins in longevity and have suggested alternative mediators for the effects of calorie restriction on longevity, including the Sir2 homolog Hst2, the kinases TOR and Sch9 and the ribosomal DNA replication fork barrier protein Fob1 (Kaeberlein et al. 2004, 2005; Lamming et al. 2005; Tsuchiya et al. 2006). Nevertheless, the dependence of sirtuins on NAD^+ provides an important link between the effects of calorie restriction on mitochondrial function and on gene expression.

3.4 Increased neurotrophic factor activity

The insulin-like growth factor IGF-1 has received much attention as a neuroprotectant, but there have been several contradictory findings similar to those previously described for PPARγ. IGF-1 has been widely shown to be neuroprotective (Cheng and Mattson, 1992; Sonntag et al. 2005 de la Monte and Wands 2005; Russo et al. 2005; Tang 2006). IGF-1 reverses age-related declines in spatial memory, prevents hydrogen peroxide and amyloid Aβ- induced neuronal death and promotes neurogenesis in aged brains (Dore et al. 1997; Markowska et al. 1998; Heck et al. 1999; Lichtenwalner et al. 2001). It is therefore quite surprising that IGF-1 levels decrease following calorie restriction in animals and humans, and that inhibition of IGF-1 signaling is associated with increased longevity (Smith et al. 1995; Rincon et al. 2005; Rasmussen et al. 2006). Moreover, the enhanced resistance of cultured fibroblasts to stress conveyed by increasing SIRT1 expression is partially reversed by IGF-1 (Cohen et al. 2004). The reasons behind this apparent discrepancy are not clear.

Unlike the effects on IGF-1, calorie restriction increases the expression of several nerve growth factors, including brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and glial cell line-derived neurotrophic factor (GDNF), most prominently in the hippocampal formation, but also in the in the basal ganglia (Lee et al. 2000, 2002b; Duan et al. 2003; Maswood et al. 2004). A diet rich in refined sugars and saturated fats reduced hippocampal BDNF levels and impaired spatial memory (Molteni et al. 2002). Interestingly, BDNF reduces food intake, and reduced BDNF signaling causes hyperphagia and obesity (Mattson 2005; Lebrun et al. 2006). It is intriguing, however, that NFκB activation can increase BDNF expression given that calorie restriction represses NFκB (Marini et al. 2004). Nevertheless, BDNF has been shown to mediate the neuroprotective effects of calorie restriction against excitotoxic injury (Duan et al. 2001a,b). BDNF promotes neuronal differentiation of embryonic and adult hippocampal progenitor cells in calorie-restricted animals and facilitates synaptic plasticity, learning and memory (Bramham and Messaoudi 2005; Lee et al. 2000, 2002a). Moreover, NT-3 and GDNF have been implicated in the antioxidant effects of calorie restriction (Thrasivoulou et al. 2006). It is also important to note that under certain experimental conditions, prolonged exposure to BDNF leads to neuronal necrosis (Kim et al. 2002, 2003), indicating that certain neuroprotective mediators may act as a double-edged sword.

3.5 Increased protein chaperone activity

Chaperones are highly conserved, ubiquitous proteins that prevent misfolding and aggregation of polypeptides into potentially toxic compounds (Hartl and Hayer-Hartl 2002; Young et al. 2004). Aberrant folding leading to the formation of insoluble aggregates has been implicated in the pathogenesis of several neurodegenerative disorders, including Alzheimer's, Parkinson's and Huntington's diseases (Agorogiannis et al. 2004; Chaudhuri and Paul 2006). In addition

to their role in polypeptide folding, chaperones - which include several families of heat shock proteins and glucose-regulated proteins - are involved in protein translocation across cellular membranes, targeting of misfolded proteins for degradation and expression of anti-apopotic and anti-inflammatory factors (Muchowski 2002; Yenari et al. 2005).

Calorie restriction increases chaperone levels in the brain as well as in several other tissues including the heart, the liver, the intestines, skeletal muscle and macrophages (Aly et al. 1994 Heydari et al. 1995; Ehrenfried et al. 1996; Moore et al. 1998; Guo et al. 2000; Frier and Locke 2005; Selsby et al. 2005; Sharma and Kaur 2005). In turn, chaperones have been shown to protect neurons in rodent and drosophila models of both acute and chronic neurological disorders such as ischemic injury, glutamate and kainate excitotoxicity, oxidative stress and toxicity secondary to phosphorylated tau protein, α-synuclein or proteins with polyglutamine expansions (Lowenstein et al. 1991; Warrick et al. 1999; Yu et al. 1999; Chan et al. 2000; Rajdev et al. 2000; Cummings et al. 2001; Auluck et al. 2002; Giffard et al. 2004; Shimura et al. 2004).

3.6 Anti-inflammatory effects

Aging and various neurological disorders are characterized by increased levels of several inflammatory mediators (Chung et al. 2002; Sarkar and Fisher 2006). NFκB activation is central component of this inflammatory process. NKκB activation can be triggered by several sources of injury such as reactive oxygen or nitrogen species or amyloid Aβ and causes enhanced transcription of interleukins (IL1β, IL2, IL4, IL6), tumor necrosis factors (TNFα and TNFβ) and the pro-inflammatory enzymes cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in various tissues, including the brain (Gloire et al. 2006; Valerio et al. 2006).

Calorie restriction reduced NFκB levels (probably a Sirt1-dependent process), blocked the synthesis of interleukins and TNFα and suppressed the activity of COX-2 and iNOS in animal models and in humans (Spaulding et al. 1997; Clement et al. 2004; Bhattacharya et al. 2006; Kalani et al. 2006; Kim et al. 2006; Ugochukwu and Figgers 2007). Intermittent fasting resulted in a reduction in seizure-induced microglial activation in a mouse model of epileptic seizures (Lee et al., 2003). Surprisingly, interferon-gamma (IFNγ), which typically activates microglial cells and promotes an inflammatory response in the brain, was increased by calorie restriction in brain and leucocytes and pretreatment of hippocampal neurons with low concentrations of IFNγ provided significant protection against excitotoxic injury (Mascarucci et la. 2002; Lee et al. 2006). Under certain experimental conditions, NFκB, interleukins and tumor necrosis factors exhibit neuroprotective and neurotrophic properties that include the promotion of neuritic outgrowth and the differentiation of progenitor cells into neurons and that possibly involve enhanced transcription of the BDNF gene (Munoz-Fernandez and Fresno 1998; Mattson and Camandola 2001; Marini et al. 2004; Widera et al. 2006). These same mechanisms might also underlie the carcinogenic potential of NFκB (Karin 2006).

NFκB exhibits apparently contradictory effects on neuronal survival, similar to many factors that are regulated by calorie restriction. NFκB comprises several regulatory subunits that can vary depending on the cell type and the presence of activators and repressors, thereby providing the means to target a large variety of genes (Perkins 2007). It is therefore highly conceivable that NFκB can mediate both neuroprotective and apoptotic processes depending on subunit composition (Kaltschmidt et al. 2005).

3.7 Enhanced neurogenesis

Neurogenesis persists in several regions of the adult brain, including the dentate gyrus, a critical region for cognition, but progressively decreases with age (Bernal and Peterson 2004; Arbous

et al. 2005). Newly generated neurons in the hippocampus might play a part in learning and memory but the functions of neural stem cells remain largely unknown (Aimone et al. 2006; Lledo et al. 2006). Calorie restriction promotes neurogenesis in adult rodents, probably by increasing BNDF levels (Lee et al. 2002a). The number of bromodeoxyuridine-positive cells in the dentate gyrus was higher in calorie restricted animals than in aged-matched controls fed *ad libidum*, indicating an increased survival of newly generated cells (Lee et al. 2002b; Bondolfi et al. 2004). However, the functional consequences of neurogenesis remain unclear.

4. The ketogenic diet

Calorie restriction in animals is achieved by either daily reduction of food intake or intermittent fasting. Both protocols induce similar physiological and metabolic changes except for one important difference: intermittent fasting leads to a much larger increase in blood levels of the ketone body β-hydroxybutyrate (Mattson et al. 2003; Mattson 2005). Interestingly, this rise in β-hydroxybutyrate concentration is associated with a more significant reduction in the vulnerability of hippocampal neurons to kainate injections. The ketogenic property of fasting was recognized several decades ago and lead to the formulation of the high-fat, low-carbohydrate ketogenic diet in the 1920s. The anticonvulsant properties of the ketogenic diet are currently well recognized, but more recent data suggests that the ketogenic diet is neuroprotective as well and that the underlying mechanisms are similar to those activated by calorie restriction (Greene et al. 2003; Kossoff 2004; Gasior et al. 2006). It is also important to note that the ketogenic diet is frequently associated with reduced caloric intake, either as part of the dietary protocol or as a consequence of the unpleasant taste of many ketogenic foods (Cullingford 2004; Bough and Rho 2007).

4.1 Neuroprotective effects of the ketogenic diet

The ketogenic diet has been shown to be effective in pharmacoresistant forms of epilepsy, including catastrophic cases of infantile spasms, the multiple seizure types associated with the Lennox-Gastaut syndrome and certain inherited metabolic disorders, with more than half the patients experiencing at least a 50% decrease in seizures (Freeman et al. 1998; Vining et al. 1998; Lefevre and Aronson 2000; Kossoff et al. 2002; Klepper et al. 2005; Caraballo et al. 2006; Eun et al. 2006; Kang et al. 2007). Furthermore, the ketogenic diet may improve long-term outcome in epileptic children beyond the dietary treatment period (Hemingway et al. 2001; Marsh et al. 2006). Similarly favorable outcomes have been reported in teenagers and adults (Sirven et al. 1999 Freeman et al. 2006).

Despite generally promising results, noteworthy side-effects have been reported with the ketogenic diet, most commonly nephrolithiasis, hyperlipidemia and slowed growth (Kwiterovich et al. 2003; Kang et al. 2004; Hartman and Vining 2007). Hyperlipidemia is of particular concern in adults because of potentially serious atherosclerotic complications. Moreover, all clinical findings relating to the ketogenic diet are based on observational studies and have not been validated in prospective clinical trials.

Notwithstanding this lack of evidence-based data, clinical observations have been replicated in several animal models of epilepsy. The ketogenic diet increased the threshold for seizures induced by amygdala kindling, GABA antagonists or pentylenetetrazole and delayed the development of spontaneous seizures in EL/Suz mice (Hori et al. 1997; Bough and Eagles 1999; Todorova et al. 2000; Bough et al. 2002; Mantis et al. 2004). Moreover, in rats exposed to kainic acid, a model of temporal lobe epilepsy, the ketogenic diet decreased both the risk of developing epilepsy and the severity of the seizures that did occur. These effects were associated with reduced hippocampal excitability and decreased supragranular mossy fiber sprouting (Muller-Schwarze et al. 1999; Stafstrom et al. 1999; Noh et al. 2003; Xu et al. 2006).

The antiepileptic effects of the ketogenic diet have been associated with improvements in cognitive function (Nordli et al. 2001; Pulsifer et al. 2001). Whether these improvements were due to improved seizure control, reduced medication or an independent, neuroprotective effect of the diet is unknown. Unexpectedly, in one study, the ketogenic diet impaired learning and memory in rats (Zhao et al. 2004). Animals were fed, however, a diet with a fat to carbohydrate plus protein ratio that was twice as high as in the standard diet – and experienced a significant retardation of brain growth. Consequently, impaired learning and memory might have been secondary to malnutrition and delayed development (Cunnane and Likhodii 2004).

With regard to calorie restriction, the neuroprotective effects of the ketogenic diet are not limited to epilepsy. In a small sample of patients with Parkinson's disease, Unified Parkinson's Disease Rating Scale scores improved by mean of 43% following treatment with the ketogenic diet for 1 month (VanItallie et al. 2005). The substitution of unsaturated for saturated fats was well tolerated and prevented the expected hypercholesterolemia in the majority of participants. Although a control group was not provided and the possible benefits of concomitant weight loss were not investigated, this study was instrumental in demonstrating the applicability of the ketogenic diet to a group of older adults suffering from a neurodegenerative disorder. Epidemiological observations based on the Rotterdam study, a longitudinal study of senior adults, are consistent with these results. Higher intake of unsaturated fatty acids was associated with a decreased incidence of Parkinson's disease (de Lau et al. 2005). Similarly, oral intake of a ketogenic medium-chain triglyceride diet improved cognitive function in patients with Alzheimer's disease (Reger et al. 2004). Preliminary data also suggest that the ketogenic diet might be beneficial in autistic children (Evangeliou et al. 2003).

Such clinical observations are supported by animal data. In mice expressing a mutant form of the human amyloid precursor protein gene, the ketogenic diet reduced the amount of soluble Aβ in brain homogenates, although performance on an object recognmition task did not improve (Van der Auwera et al. 2005). The ketogenic diet also reduced contusion volume following head trauma and neuronal loss secondary to insulin-induced hypoglycemia (Prins et al. 2005; Yamada et al. 2005). Finally, in transgenic mice expressing a mutated superoxide dismutase 1, a model of amyotrophic lateral sclerosis, the ketogenic diet delayed the progression of motor deficits and decreased motor neuron loss in the spinal cord (Zhao et al. 2006).

4.2 Neuroprotective mechanisms of the ketogenic diet

The ketogenic diet has been associated with antioxidant effects in several studies. First, mitochondria from animals fed a ketogenic diet produced lower amounts of reactive oxygen species in isolated mitochondria (Sullivan et al. 2004b). Second, the ketogenic diet increased glutathione peroxidase activity in the hippocampus (Ziegler et al. 2003). Third, the ketogenic diet increased UCP expression and activity in the hippocampus, thereby decreasing mitochondrial membrane potential and, as a consequence, diminishing the production of reactive oxygen species (Sullivan et al. 2004b). The ketogenic diet also stimulated mitochondrial biogenesis and increases cerebral ATP and phosphocreatine concentrations, suggesting increased metabolic efficiency (DeVivo et al. 1978; Bough et al. 2006). Further, genes encoding bioenergetic enzymes are upregulated by the ketogenic diet (Noh et al. 2005; Bough et al. 2006). The combination of these mechanisms suggests that, as with calorie restriction, mitochondria are an important target of ketogenic diet action.

In addition to antioxidant and metabolic effects, anti-apoptotic mechanisms have been implicated, including decreased expression of the pro-apoptotic factors clusterin and caspase-3 in animals exposed to kainic acid, as well as increased activity of calbindin, an intracellular calcium buffer (Noh et al. 2003, 2005a,b). The ketogenic diet also inhibited the dissociation of the pro-apoptotic factor Bad from the chaperone protein 14-3-3, a process implicated in

kainate-induced epileptogenesis (Noh et al. 2006b). In parallel to these neuroprotective actions, the ketogenic diet might further prevent brain damage by limiting neuronal excitability. The ketogenic diet increased the levels of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and the expression of glutamic acid decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis (Cheng et al. 2004; Dahlin et al. 2005; Yudkoff et al. 2005) in rodent brain. However, it remains unclear whether the observed changes result in an anticonvulsant effect, particularly since GABA levels were elevated in non-seizure-prone areas of the brain, and increases in GAD levels do not necessarily translate to increased GABA production. Interestingly, the anticonvulsant effects of the ketogenic diet may also involve noradrenergic signaling (Szot et al. 2001; Martillotti et al. 2006).

Some of the neuroprotective effects of the ketogenic diet might be mediated by polyunsaturated fatty acids. Specifically, brain and serum levels of polyunsaturated fatty acids that exhibit anticonvulsant and neuroprotective properties (e.g., docosahexaenoic acid) increase following treatment with the ketogenic diet (Fraser et al. 2003; Taha et al. 2005; Bazan 2007). Polyunsaturated fatty acids decrease the excitability of hippocampal neurons and increase neuronal survival following traumatic, ischemic and excitotoxic injuries (Xiao and Li 1999;Lauritzen et al. 2000; Young et al. 2000; Strokin et al. 2006; King et al. 2006). Alternatively, there is evidence that ketone bodies - products of fatty acid catabolism - themselves can mediate neuroprotective effects similar to that of the ketogenic diet, and possibly calorie restriction as well (see section 5.1 below)

5. Ketone bodies

Despite mounting evidence supporting the anticonvulsant and neuroprotective effects of ketogenic diets, their relative unpalatability and the risk of systemic complications - particularly in adults - preclude more widespread implementation. A safer alternative has long been sought after. During conditions of reduced glucose availability, energy is derived from the conversion of fats to ketone bodies, mainly β-hydroxybutyrate and acetoacetate, and, to a lesser extent, acetone (Laffel 1999). The liver is the main site of ketone body synthesis, although astrocytes can also produce ketone bodies from fats (Guzman and Blazquez 2004).

Following a day of fasting or exposure to the ketogenic diet, ketone bodies reach low millimolar concentrations in the blood, with cerebrospinal levels being moderately lower (Haymond et al. 1982; Lamers et al. 1995; Seymour et al. 1999; Thavendiranathan et al. 2000). Ketone bodies cross the blood-brain barrier through proton-linked, monocarboxylic acid transporters and then enter neurons by diffusion or through monocarboxylic acid transporters (Nehlig 2004; Morris 2005). Fasting and the ketogenic diet increase the permeability of the blood-brain barrier to ketones and enhance the expression of monocarboxylic acid transporters. The ketogenic diet also enhances glial proliferation in the CA3 region of the hippocampus (Silva et al. 2005). The observed gliosis is not associated with any functional deficits and might in fact constitute a means of increasing ketone body synthesis.

5.1 Neuroprotective effects of ketone bodies

Anticonvulsant effects have been demonstrated for acetoacetate and acetone but not for β-hydroxybutyrate. First, both acetoacetate and acetone decreased the incidence of seizures triggered by loud auditory stimuli in Frings audiogenic-susceptible mice (Rho et al. 2002). Second, acetone suppressed seizures in several additional models of epilepsy, including the amygdala kindling, maximal electroshock and pentylenetetrazole tests (Likhodii et al. 2004).

In animal models of Parkinson's disease, chronic subcutaneous infusion of β-hydroxybutyrate in mice conferred partial protection against dopaminergic cell loss and motor deficits induced by MPTP (Tieu et al. 2003). β-hydroxybutyrate also protected cultured mesencephalic

dopaminergic neurons from the toxic effects of MPTP and rotenone, another inhibitor of mitochondrial complex I (Kashiwaya et al. 2000; Imamura et al. 2006). In patients with Alzheimer's disease, administration of medium-chain triglycerides improved memory and the degree of improvement correlated with blood levels of β-hydroxybutyrate (Reger et al. 2004). Further, direct application of β-hydroxybutyrate protected cultured hippocampal neurons against Aβ toxicity (Kashiwaya et al. 2000). Finally, exogenous administration of either β-hydroxybutyrate or acetoacetate reduced neuronal loss and improved neuronal function in animal models of hypoxia, hypoglycemia and focal ischemia (Suzuki et al. 2001, 2002; Massieu et al. 2001, 2003; Masuda et al. 2005).

More recently, the neuroprotective effects of ketone bodies were demonstrated in two experimental models relevant to several neurological diseases - glutamate excitotoxicity and oxidative stress. Glutamate excitotoxicity is a pathogenic process that can lead to calcium-mediated neuronal injury and death by generating reactive oxygen species and by impairing mitochondrial bioenergetic function (Emerit et al. 2004; Mattson and Magnus 2006). Oxidative stress subsequently damages nucleic acids, proteins and lipids and potentially opens the mitochondrial permeability transition pore which, in turn, can further stimulate ROS production, worsen energy failure and release pro-apoptotic factors such as cytochrome c into the cytoplasm (Kowaltowski et al 2001; Nicholls 2004).

A combination of β-hydroxybutyrate and acetoacetate (1 mM each) increased the survival of acutely dissociated rat neocortical neurons exposed to glutamate or hydrogen peroxide for 10 min or more (Kim et al. 2007; Maalouf et al. 2007b). Increased survival was associated with the inhibition of electrophysiological signs of neuronal injury, specifically, irreversible depolarization associated with a significantly decreased membrane resistance. Acetoacetate (also in millimolar concentrations) had a similar effect in primary hippocampal cultures (Noh et al. 2006a). In addition, the combination of β-hydroxybutyrate and acetoacetate prevented oxidative impairment of long-term potentiation in the CA1 region of the hippocampus, indicating that ketone bodies not only limited neuronal loss but also preserved synaptic function (Maalouf et al. 2007a).

5.2 Neuroprotective mechanisms of ketone bodies

Initial attempts to determine the anticonvulsant mechanisms of ketone bodies have been unrevealing. In electrophysiological experiments, low millimolar concentrations of β-hydroxybutyrate and acetoacetate did not affect neuronal excitability or synaptic transmission in the hippocampus (Thio et al. 2000). More recent evidence, however, suggests that other subcortical structures may be critically involved in modulation of seizure activity. Millimolar concentrations of β-hydroxybutyrate and acetoacetate reduced the spontaneous firing of neurons in the substantia nigra pars reticulata, an effect that required the opening of ATP-sensitive potassium (K_{ATP}) channels (Ma et al. 2007). However, the significance of this effect remains unclear, especially since ketone bodies are known to raise ATP levels which would shut down K_{ATP} channels. Despite this intriguing observation, ketone bodies have been mostly studied from the standpoint of antioxidant and metabolic effects. A combination of β-hydroxybutyrate and acetoacetate (1 mM each) decreased the production of reactive oxygen species by complex I of the mitochondrial respiratory chain (Maalouf et al. 2007b). Specifically, in acutely isolated rat neocortical neurons, increases in the intracellular levels of superoxide following prolonged exposure to glutamate were inhibited by pretreatment with ketone bodies. Ketone bodies also decreased reactive oxygen species concentrations in isolated mitochondria overloaded with calcium. In a similar study, increased survival of HT22 hippocampal cell lines treated with acetoacetate was associated with decreased production of reactive oxygen species (Noh et al. 2006a).

In the study by Maalouf et al. (2007b), ketone bodies decreased NADH levels in intact neurons and in isolated mitochondria but did not affect glutathione levels. Furthermore, ketone bodies prevented the inhibition of mitochondrial respiration by calcium in the presence of pyruvate and malate but not succinate. Given that NADH oxidation correlates with decreased mitochondrial formation of reactive oxygen species (Duchen, 1992; Kudin et al, 2004; Sullivan et al, 2004a) and that pyruvate and malate drive mitochondrial respiration through complex I, the source of reactive oxygen species in neurons (Turrens 2003), these findings strongly suggested that ketone bodies decreased the production of reactive oxygen species by enhancing complex I-driven mitochondrial respiration rather than increase antioxidant factors such as glutathione.

Consistent with the observed improvements in mitochondrial respiration, β-hydroxybutyrate increased ATP production substantially in isolated brain mitochondria and brain homogenates and acetoacetate increased phosphocreatine levels in cardiac myocytes (Suzuki et al. 2001; Squires et al. 2002 Tieu et al. 2003). These findings provide further support for the hypothesis that ketone bodies improve mitochondrial function and explain how ketone bodies increase myocardial hydraulic work and sperm motility described in previous work (Veech et al. 2001; Veech 2004). These findings also suggest that ketone bodies and calorie restriction enhance mitochondrial function through similar mechanisms.

An additional feature shared by ketone bodies, the ketogenic diet and calorie restriction is the inhibition of apoptosis. Ketone bodies prevented neuronal injury and death caused by hydrogen peroxide or by the glutathione oxidant diamide (Kim et al. 2007). Their neuroprotective effect was replicated by inhibitors of mitochondrial permeability transition. In addition, ketone bodies elevated the threshold for calcium-induced mitochondrial permeability transition in isolated brain mitochondria. Mitochondrial permeability transition can be triggered by various pathological menchanisms, most notably oxidative stress, causing the cytoplasmic release of cytochrome c and the subsequent induction of caspase-mediated apoptosis (Mattson et al. 2003; Nicholls 2004; Balaban et al. 2005). In support of these data, ketone bodies blocked the activation of the apoptotic enzyme serine/threonine phosphatase 2A by oxidative stress (Maalouf et al. 2007a).

Protein phosphatase 2A is a serine-threonine protease enzyme that can trigger apoptosis by inactivating the anti-apoptotic factor Bcl2, an inhibitor of mitochondrial permeability transition (Virshup 2000; Janssens and Goris 2001; Dagda et al. 2003; Kroemer et al. 2007). Protein phosphatase 2A activation occurs following the conversion of sphingomyelin, a membrane constituent, to ceramide in a series of biochemical reaction that are facilitated by reactive oxygen species and inhibited by antioxidants such as glutathione (Zabrocki et al. 2002; Sultan et al. 2006; Won and Singh 2006). Consistently, ceramide induced Bcl-2 dephosphorylation and cytochrome c release from mitochondria (Richter and Ghafourifar 1999; Ruvolo et al. 1999, 2002). In addition to triggering apoptosis, protein phosphatase 2A inhibited long-term potentiation (Fukunaga et al., 2000; Kang-Park et al., 2003). Ketone bodies were recently shown to prevent oxidative impairment of long-term potentiation, an effect that was associated with inhibition of protein phosphatase 2A (Maalouf et al. 2007a).

6. Conclusion

Calorie restriction and the ketogenic diet share two characteristics: reduced carbohydrate intake and a compensatory rise in ketone bodies. The neuroprotective effects of reduced carbohydrate per se are being investigated by several research groups (Mattson et al. 2003; Ingram et al. 2006). We have evaluated the possibility that ketone bodies might mediate the neuroprotective effects of calorie restriction and of the ketogenic diet. An expanding body of evidence indicates that ketone bodies are indeed neuroprotective and that the underlying mechanisms are similar

to those associated with calorie restriction - specifically at the mitochondrial level. However, several important questions remain unanswered. The effects of ketone bodies on gene expression have not been investigated, although inhibition of glycolysis with 2-deoxyglucose (which blocks phosphofructose isomerase) has been reported to inhibit BDNF expression and kindling progression in rats (Garriga-Canut et al, 2006). Moreover, the neuroprotective of ketone bodies *in vivo* have not been thoroughly examined. For instance, it is imperative to demonstrate that the neuroprotective effects of ketone bodies are associated with a preservation of clinically relevant functions such as cognition. Finally, it is crucial to determine if the anti-apoptotic properties of ketone bodies might potentially increase the risk of carcinogenesis. Intriguingly, both the calorie restriction and the ketogenic diet have been associated with anti-neoplastic properties and similarly, preliminary data suggest that the ketone bodies β-hydroxybutyrate and acetoacetate have anti-neoplastic effects on human glioblastoma cell lines (Patel et al. 2004; Jolly 2006 Zhou et al. 2007). Further research will hopefully further clarify the mechanisms underlying the neuroprotective properties of calorie restriction and ketone bodies and explain the counter-intuitive effects on carcinogenesis.

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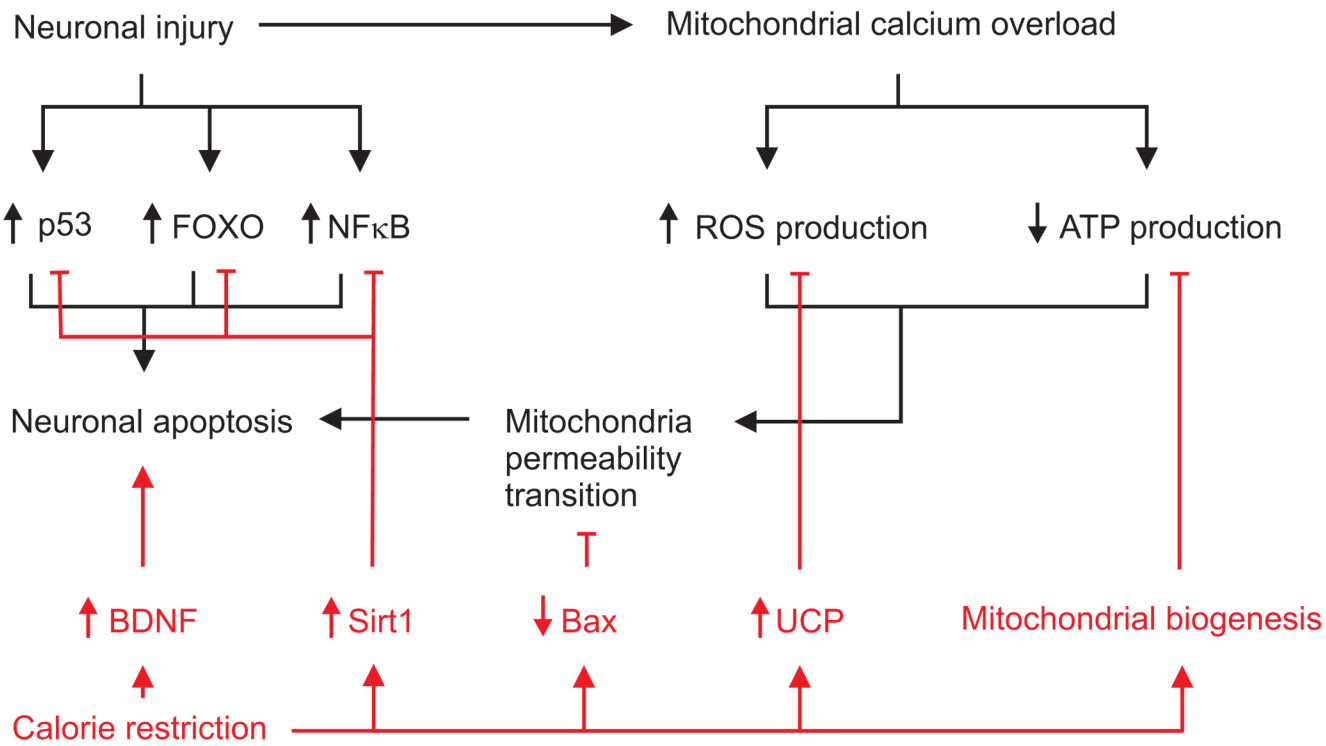

Figure 1.
Mechanisms underlying the neuroprotective effects of calorie restriction. Neuronal injury, either acute (for example following ischemia) or chronic (such as amyloid toxicity) impairs mitochondrial function, resulting in increased formation of reactive oxygen species (ROS) and decreased ATP synthesis, and activates apoptotic pathways. Calorie restriction abrogates mitochondrial impairment, inhibits apoptotic pathway (mainly by activating Sirt1) and increases neurotrophic activity, thereby increasing neuronal resistance to injury.

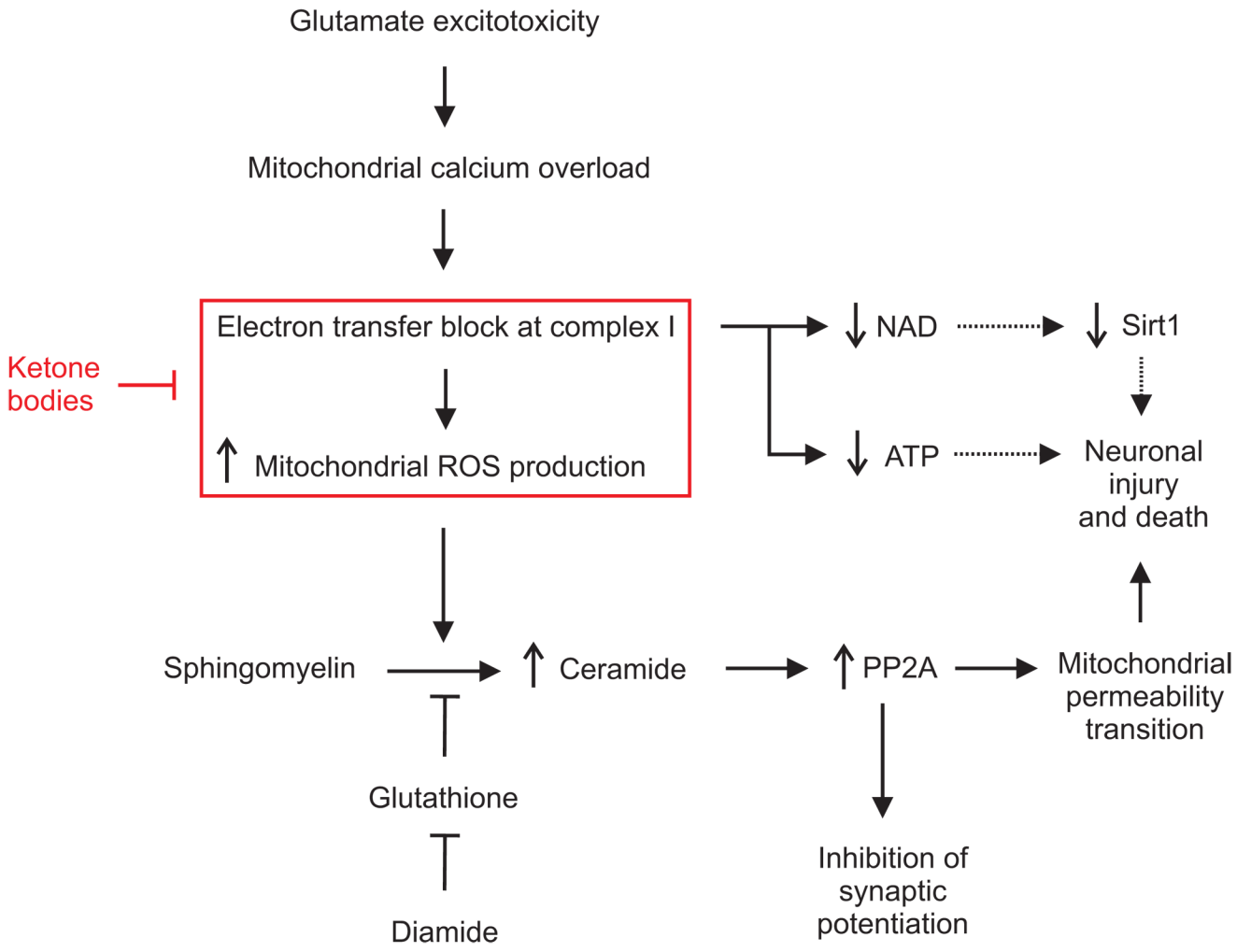

Figure 2.
Mechanisms underlying the neuroprotective effects of ketone bodies. Ketone bodies improve mitochondrial respiration and, as a result, increase NAD levels relative to NADH, decrease reactive oxygen species (ROS) formation and enhance ATP production. Ketone bodies also decrease the activity of the apoptotic enzyme protein phosphatase 2A (PP2A), possibly by inhibiting the ROS-dependent formation of ceramide, a PP2A activator. Sirt1 involvement is possible given the increased NAD to NADH ratio, but this has yet to be demonstrated.