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Review

The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies

Marwan Maalouf^{a,*}, Jong M. Rho^b, Mark P. Mattson^c

^aDepartment of Neurobiology, David Geffen School of Medicine, University of California, 63-323 CH5, Box 951763, Los Angeles, CA 90095-1763, USA

^bBarrow Neurological Institute and St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

^cLaboratory of Neurosciences, National Institute on Aging, Intramural Research Program, Baltimore, MD, USA

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ABSTRACT

Both calorie restriction and the ketogenic diet possess broad therapeutic potential in various clinical settings and in various animal models of neurological disease. Following calorie restriction or consumption of a ketogenic diet, there is notable improvement in mitochondrial function, a decrease in the expression of apoptotic and inflammatory mediators and an increase in the activity of neurotrophic factors. However, despite these intriguing observations, it is not yet clear which of these mechanisms account for the observed neuroprotective effects. Furthermore, limited compliance and concern for adverse effects hamper efforts at broader clinical application. Recent research aimed at identifying compounds that can reproduce, at least partially, the neuroprotective effects of the diets with less demanding changes to food intake suggests that ketone bodies might represent an appropriate candidate. Ketone bodies protect neurons against multiple types of neuronal injury and are associated with mitochondrial effects similar to those described during calorie restriction or ketogenic diet treatment. The present review summarizes the neuroprotective effects of calorie restriction, of the ketogenic diet and of ketone bodies, and compares their putative mechanisms of action.

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* Corresponding author.

E-mail address: marwan.maalouf@ucla.edu (M. Maalouf).

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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 biochemical effects of fasting, has been challenging to use in clinical settings despite proven efficacy. Consequently, there is now considerable effort expended to understand the mechanisms underlying the neuroprotective effects of calorie restriction and of the ketogenic diet with the hope of developing alternative therapeutic options. The present article reviews findings supporting the neuroprotective effects of calorie restriction and of the ketogenic diet, summarizes the mechanisms activated by these diets and proposes that ketone bodies could possibly replicate some of their neuroprotective properties by activating common mechanisms at the mitochondrial level.

2. Calorie restriction

2.1. Neuroprotective effects of calorie restriction

2.1.1. Human studies of calorie restriction

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 hallmarks of pathological brain aging – are more common in obese patients (Jagust et al., 2005). In contrast, apart from the well-known effects of fasting on seizure frequency, low dietary energy intake is associated with

enhanced longevity (Redman et al., 2008) and decreased incidence of Alzheimer's and Parkinson's diseases (e.g., the New York City cohort). Further, 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 healthcare 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 restriction on brain aging and neurological disease have not been performed, and all available information is derived exclusively from animal studies.

2.1.2. Animal studies of calorie restriction

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 diminished by calorie restriction in rodents (Mattson et al., 2003; Mattson and Magnus, 2006). Rats placed on a hypo-caloric diet from the age of 3 weeks, and tested at 2 years of age, perform significantly better than aged-matched controls fed *ad libitum* on both spatial (i.e., 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 Algeri, 1992). Calorie-restricted middle-aged and aged mice exhibit similar improvements in learning tasks that also include active and passive avoidance learning (Ingram et al., 1987; Means et al., 1993; Hashimoto and Watanabe, 2005). In parallel, calorie restriction also prevents age-related deficits in hippocampal long-term potentiation (LTP), 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 – a mixed genetic-environmental model of stimulus-induced epilepsy, the onset of seizures

typically occurs in the first few months of life, but is delayed for several weeks by calorie restriction (Greene et al., 2001; Mantis et al., 2004). Calorie restriction also elevates the threshold to seizures elicited by tail-vein infusion of pentylene-tetrazole, a γ -aminobutyric acid_A (GABA_A) receptor antagonist (Eagles et al., 2003). Consistently, rats on a calorie-restricted diet exhibit 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 prevents spatial learning deficits in rats exposed to excitotoxic injury, and improved cognitive function correlates with decreased neuronal death in the hippocampus (Bruce-Keller et al., 1999).

In animal models of Parkinson's disease, calorie restriction improves motor function and enhances neuronal survival in the substantia nigra of mice and monkeys exposed to MPTP, a neurotoxin converted to MPP⁺ in astrocytes. Subsequently, MPP⁺ is transported into dopaminergic neurons, where it inhibits NADH dehydrogenase and increases reactive oxygen species (ROS) formation at complex I of the mitochondrial respiratory chain (Duan and Mattson, 1999; Maswood et al., 2004). A comparable, neuroprotective effect has been reported in the striatum of mice treated with 3-nitropropionic acid, a succinate dehydrogenase (complex II) inhibitor that causes motor and histological defects similar to those seen in Huntington's disease (Bruce-Keller et al., 1999). Calorie restriction also attenuates amyloid deposition in monkeys and in transgenic mouse models of Alzheimer's disease (Patel et al., 2004; Qin et al., 2006a,b), ameliorates cognitive deficits in a mouse model of Alzheimer's disease (Halagappa et al., 2007), and reduces neuronal loss in neocortex, hippocampus and striatum of rats subjected to a 30-minute, cerebral four-vessel occlusion model of ischemic stroke (Marie et al., 1990). Similarly, feeding rats on alternate days decreases infarct size and improves motor function following middle cerebral artery occlusion for 1 h (Yu and Mattson, 1999). Finally, calorie restriction decreases neuronal loss and improves functional recovery following traumatic brain or spinal cord lesions, even when started after 24 h after the injury (Davis et al., 2008; Plunet et al., in press).

Although calorie restriction appears to exert beneficial effects in most studies of aging and neurological disease, an absence of such clinical effects (and complications) is reported. First, several studies have failed to reveal any influence of calorie restriction on spatial learning in both rats and mice (Bellush et al., 1996; Markowska, 1999; Hansalikh et al., 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 amyotrophic lateral sclerosis (ALS) mutation, age of onset of paralysis was unaffected, 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 amongst the different

strains within a single species might influence differential 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.

2.2. Neuroprotective mechanisms of calorie restriction

There are several mechanisms proposed to explain the neuroprotective effects of calorie restriction (Fig. 1). These mechanistic theories can be grouped into two general categories: 1) improved mitochondrial function, leading to decreased production of ROS and increased energy output; 2) regulation of gene expression, resulting in decreased activity of pro-apoptotic and inflammatory factors and increased levels of neuroprotective factors such as neurotrophins and molecular chaperones. Current hypotheses are generally based, however, on studies of longevity rather than neuroprotection and on data from primitive organisms or non-neuronal mammalian tissue. Moreover, there is considerable variability in the available data. In particular, several mechanisms that increase overall longevity in response to calorie restriction might have the opposite effect on neuronal survival and resistance to injury. Nevertheless, we believe that data gathered from research on longevity provide valuable insights into the neuroprotective properties of calorie restriction and generate a useful framework for future studies.

2.2.1. Antioxidant effects

Although ROS are by cytoplasmic oxygenases in response to increased intracellular calcium concentrations, mitochondria are the major source of ROS, 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 damage—for example, following 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 peroxidized 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 enhances 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

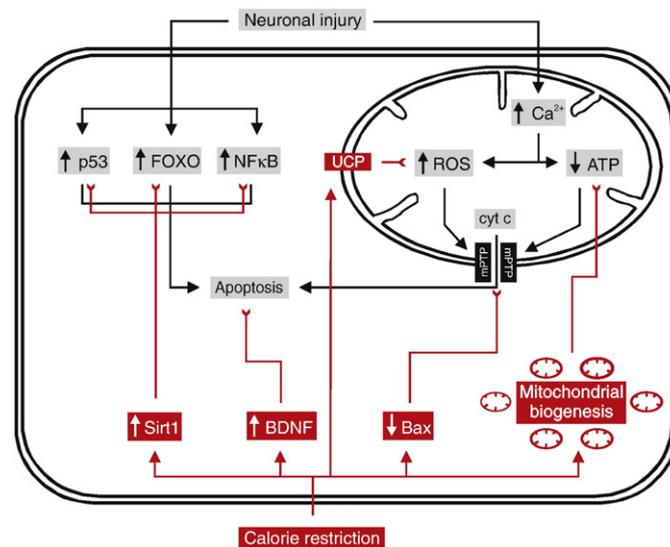


Fig. 1 – Mechanisms underlying the neuroprotective effects of calorie restriction. Neuronal injury, either acute (e.g., following ischemia) or chronic (e.g., due to amyloid toxicity), disrupts calcium homeostasis, impairs mitochondrial function, increases formation of reactive oxygen species (ROS) and decreases ATP synthesis. Consequently, opening of the mitochondrial permeability transition pore (mPTP) leads to cytochrome c (cyt c) release into the cytoplasm and activation of the apoptotic cascade. Calorie restriction decreases ROS levels by activating uncoupling proteins (UCP), increases neurotrophic (BDNF) activity and stimulates Sirt1. In turn, Sirt1 inhibits apoptotic (Bax, p53 and FOXO) and inflammatory (NFκB) factors and promotes mitochondrial biogenesis, thereby restoring ATP levels. Apoptotic pathways are depicted in black and neuroprotective pathways are shown in red. Dark arrows indicate excitatory effects whereas inverted arrows are inhibitory.

et al., 1994; Deruisseau et al., 2006). Second, a decrease in the mitochondrial production of ROS 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 libitum* 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 calorie restriction actually decreases mitochondrial production of ROS is unclear, but the mechanism may involve uncoupling proteins (UCPs) 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 ROS (Harper et al., 2004; Andrews et al., 2005; Bevilacqua et al., 2005; Krauss et al., 2005; Lopez-Lluch et al., 2006). Consistently, enhanced UCP activity has been associated with increased longevity and neuronal resistance to ischemic, toxic, traumatic and epileptic injury (Mattiasson et al., 2003; Sullivan et al., 2003; Andrews et al., 2006; Conti et al., 2005, 2006; Liu et al., 2006). Further, mild mitochondrial uncoupling using the protonophore 2,4-dinitrophenol decreases ROS levels and enhances longevity (Caldeira da Silva et al., in press).

2.2.2. 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 ROS, 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-Pinto 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 invoking uncoupling proteins, this discrepancy can be explained by the fact that calorie restriction also promotes mitochondrial biogenesis, thereby maintaining total metabolic output per cell while decreasing mitochondrial production of ROS (Diano et al., 2003; Nisoli et al., 2005; Civitarese et al., 2007; Valle et al., 2008).

The neuroprotective benefits of this increased metabolic efficiency, which allows neurons to preserve total metabolic output despite the decrease in calorie intake, have not been directly investigated but would be expected to increase neuronal resistance to injury, especially given that mitochondrial damage and energy failure are central components of many neurological disorders (Green and Kroemer, 2004; Patel et al., 2004; Moro et al., 2005; Martin, 2006; Onyango and Khan, 2006).

2.2.3. 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; Marmorstein, 2004; Sauve et al., 2006). Increased Sir2 activity lengthens life span and calorie restriction increases Sir2 levels but 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 nicotinamidase that would alleviate nicotinamide-mediated inhibition (Anderson et al., 2002, 2003; Gallo et al., 2004). These findings only apply, however, to the active replication (i.e., mitotic) phase but not to the chronological (post-mitotic) phase of the yeast life span, even though calorie restriction is known to extend both phases (Bitterman et al., 2003; Fabrizio and Longo, 2003; Longo and Kennedy, 2006).

Before dying, yeast cells undergo a specific number of divisions, and this number is a measure of the replicative life span. Yeast cells actively replicate only when nutrients are abundant. In contrast, chronological life span indicates the amount of time yeast cells survive without dividing following nutrient deprivation. Yeast cells can actually remain viable for weeks (and possibly longer) in a hypo-metabolic state when nutrients are scarce. Therefore, to study chronological life span, yeast cells are usually 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 decreases amyloid A β 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 decreases A β toxicity in neuroblastoma and PC12 cells (Jang and Surh, 2003; Savaskan et al., 2003). Moreover, resveratrol reduces

neuronal dysfunction and death in nematode and murine models of Huntington's disease. The neuroprotective effects of resveratrol can also be seen in *C. elegans* by increasing the dosage of Sir2.1, the nematode Sir2 ortholog, and can be 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*) has also been attributed to increased Sirt1 activity (Araki et al., 2004). In contrast, Sirt1 deficiency and nicotinamide, a sirtuin inhibitor, prolong the replicative life spans of mouse embryonic and human fibroblasts chronically exposed to sub-lethal oxidative stress (Chua et al., 2005; Lim et al., 2006). Increased Sirt1 activity however prevents apoptosis of mouse embryonic and human fibroblasts following acute administration of hydrogen peroxide at higher doses and following acute DNA damage (Luo et al., 2001; Chua et al., 2005). The reasons behind these seemingly contradictory effects of Sirt1 in fibroblasts remain unclear.

Several mechanistic hypotheses have been advanced 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 (PPAR γ); and the nuclear factor NF κ B (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 yet been directly demonstrated 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). Furthermore, Sirt1 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 PPAR γ 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 PPAR γ is neuroprotective (Bordet et al., 2006; Sundararajan et al., 2006). PPAR γ agonists reduce neuronal death secondary to NMDA excitotoxicity (Zhao et al., 2006a), infarct size following middle cerebral artery occlusion (Pereira et al., 2005, 2006; Shimazu et al., 2005; Sundararajan et al., 2005), A β 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 (Bredert et al., 2002). Furthermore, PPAR γ agonists improve cognitive function in patients with Alzheimer's disease (Watson et al., 2005; Risner et al., 2006), enhance motor function and delay death in murine models of amyotrophic lateral sclerosis (Kiaei et al., 2005; Schutz et al., 2005) and reduce clinical severity in experimental allergic

encephalomyelitis, a model of multiple sclerosis (Niino et al., 2001; Feinstein et al., 2002; Natarajan et al., 2003). PPAR γ has also been shown to stimulate neural stem cell growth and differentiation (Wada et al., 2006).

The mechanism of action of PPAR γ that has received the most attention is decreased expression of inflammatory factors (Daynes and Jones, 2002). This anti-inflammatory effect involves NF κ B inhibition (Poynter and Daynes, 1998; Hu et al., 2005; Pereira et al., 2005). It should be noted, however, that Sirt1 also deacetylates NF κ B (Yeung et al., 2004). Therefore, NF κ B repression by Sirt1 might compensate for the concomitant inhibition of PPAR γ by Sirt1. Unfortunately, it is not clear if this combination of changes results in an overall neuroprotective effect because NF κ B 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 up-regulates 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).

In summary, Sirt1 activation is associated with molecular mechanisms that appear contradictory and that might differ from those of calorie restriction. Nevertheless, the dependence of sirtuins on NAD⁺ provides an important link between the effects of calorie restriction on mitochondrial function and on gene expression. This link is reinforced by the recent discovery that Sirt1 activation promotes mitochondrial biogenesis and that resveratrol exhibits antioxidant properties in various cell types and experimental models of injury (Anekonda, 2006; Anekonda and Reddy, 2006; Guarente, 2008). The underlying molecular pathway probably involves Sirt1-mediated deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 α), a transcriptional coactivator of nuclear genes encoding mitochondrial proteins (Nemoto et al., 2005; Rodgers et al., 2008).

2.2.4. 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 PPAR γ . 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 A β -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 basal ganglia (Lee et al., 2000, 2002b; Duan et al., 2003; Maswood et al., 2004; Thrasivoulou et al., 2006). In contrast, a diet rich in refined sugars and saturated fats reduces hippocampal BDNF levels and impairs spatial memory (Molteni et al., 2002). Furthermore, decreased BDNF signaling causes hyperphagia and obesity whereas BDNF diminishes food intake (Mattson, 2005; Lebrun et al., 2006). It is intriguing to note, however, that NF κ B activation can increase BDNF expression given that calorie restriction represses NF κ B (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).

Interestingly, Garriga-Canut et al. (2006) found that 2-deoxy-D-glucose (2-DG), a phosphoglucose isomerase inhibitor being investigated as a potential calorie restriction mimetic, reduced seizure progression in the rat kindling model of temporal lobe epilepsy by decreasing hippocampal expression of BDNF and its receptor tyrosine kinase B (TrkB). Consistently, acute infusions of BDNF in the hippocampus accelerate kindling development and deletion of TrkB gene prevents epileptogenesis in that same model (He et al., 2004; Xu et al., 2004). Furthermore, 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 double-edged swords.

2.2.5. 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-apoptotic 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 (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 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). Interestingly however, one study found that expression of genes encoding heat shock proteins actually decreased following calorie restriction of aged animals (Park and Prolla, 2005). The reasons behind these seemingly contradictory effects are unknown.

2.2.6. 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). NF κ B activation is central component of this inflammatory process. NF κ B activation can be triggered by several sources of injury, such as reactive oxygen or nitrogen species or amyloid A β , and causes enhanced transcription of interleukins (IL1 β , IL2, IL4, IL6), tumor necrosis factors (TNF α and TNF β) 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 reduces NF κ B levels (probably through a Sirt1-dependent process), blocks the synthesis of interleukins and TNF α and suppresses 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 results in a reduction of seizure-induced microglial activation in a mouse model of epileptic seizures (Lee et al., 2003). Surprisingly, interferon-gamma (IFN γ), which typically activates microglial cells and promotes an inflammatory response in the brain, is increased by calorie restriction in brain and leucocytes, and pretreatment of hippocampal neurons with low concentrations of IFN γ provides significant protection against excitotoxic injury (Mascarucci et al., 2002; Lee et al., 2006). Under certain experimental conditions, NF κ B, 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 NF κ B (Karin, 2006).

NF κ B exhibits apparently contradictory effects on neuronal survival, similar to many factors regulated by calorie restriction. These contradictory findings may be reconciled, however, by the fact that NF κ B 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 NF κ B can mediate both neuroprotective and apoptotic processes depending on subunit composition (Kaltschmidt et al., 2005).

2.2.7. 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; Abrous 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 BDNF levels (Lee et al., 2002a). The number of bromodeoxyuridine-positive cells in the dentate gyrus is higher in calorie-restricted animals than in aged-matched controls fed *ad libitum*, indicating an increased survival of newly generated cells (Lee et al., 2002b; Bondolfi et al., 2004). However, the functional consequences of neurogenesis remain unclear.

2.2.8. Hormesis

Calorie restriction is associated with multiple and apparently independent (or even contradictory) mechanisms. Recent studies have attempted to reconcile these effects by suggesting that many of the benefits of calorie restriction on the nervous system result from a widespread activation of adaptive cellular stress responses, a process called hormesis (Calabrese et al., 2007; Mattson 2008a,b). 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- κ B (Mattson and Cheng, 2006). 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 calorie 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 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 up-regulated 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. The ketogenic diet

Calorie restriction in animals is achieved by either daily reduction of food intake or by 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 effect of fasting was appreciated nearly a century ago, and led to the formulation of the high-fat, low-carbohydrate ketogenic diet in the 1920s.

Currently, the anticonvulsant properties of the ketogenic diet are well recognized, but available data suggest that the ketogenic diet is also neuroprotective and that some of the underlying mechanisms are similar to those activated by calorie restriction (Greene et al., 2003; Kossoff 2004; Gasior et al., 2006). It is important to note, however, that the ketogenic

diet is frequently associated with reduced calorie intake, either as part of the dietary protocol or as a consequence of the unpleasant taste of some ketogenic foods (Cullingford 2004; Bough and Rho 2007).

3.1. Neuroprotective effects of the ketogenic diet

The ketogenic diet is clinically effective in pharmaco-resistant forms of epilepsy, including catastrophic cases of infantile spasms, the multiple seizure types associated with the Lennox–Gastaut syndrome, and certain inherited metabolic disorders. More than half the patients are 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). The ketogenic diet may also improve long-term outcome in epileptic children beyond the dietary treatment period (Hemingway et al., 2001; Marsh et al., 2006). Similar favorable outcomes have been reported in teenagers and adults (Sirven et al., 1999; Freeman et al., 2006). Furthermore, ketogenic diet use has been associated with improvements in cognitive function (Nordli et al., 2001; Pulsifer et al., 2001). Whether these improvements are due to improved seizure control, reduced medication or an independent, neuroprotective effect of the diet is unknown.

The anticonvulsant efficacy of the ketogenic diet was recently confirmed in a prospective, randomized controlled trial involving children and teenagers with uncontrolled seizures (Neal et al., 2008b). Both generalized and focal epilepsies were included. Following 3 months of treatment, patients on the ketogenic diet exhibited significantly less seizures than those on a regular diet. Several side-effects were noted, most importantly height and weight retardation (Neal et al., 2008a). Growth retardation was not prevented by the use of a medium-chain triglyceride diet, even though the group on this diet consumed significantly more proteins.

Clinical efficacy of the ketogenic diet has been further validated in several animal models of epilepsy. The ketogenic diet increases the threshold for seizures induced by amygdala kindling, GABA antagonists (such as pentylenetetrazole) and delays the development of seizures in EL and in flurothyl-treated mice (Hori et al., 1997; Bough and Eagles 1999; Rho et al., 2002; 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 decreases both the risk of developing epilepsy and the severity of the seizures that do occur. These effects are 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). Unexpectedly however, in one study, the ketogenic diet impaired learning and memory in rats (Zhao et al., 2004). Animals experienced a significant retardation of brain growth as well, but were fed a diet with a fat-to-carbohydrate plus protein ratio that was twice as high as in the standard diet. Consequently, impaired learning and memory might have been secondary to malnutrition and delayed development (Cunnane and Likhodii 2004).

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

(UPDRS) scores improved by a 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. In addition to the lack of a control group, the effect of the ketogenic diet on levodopa absorption was not considered, and the possible benefits of concomitant weight loss were not investigated. Notwithstanding these caveats, 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 is associated with a decreased incidence of Parkinson's disease (de Lau et al., 2005). Similarly, oral intake of a ketogenic medium-chain triglyceride diet improves 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 (Evangelou 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 A β in brain homogenates, although performance on an object recognition task did not improve (Van der Auwera et al., 2005). The ketogenic diet also decreased contusion volume following head trauma and neuronal loss secondary to insulin-induced hypoglycemia (Prins et al., 2005; Yamada et al., 2005). Similarly, in rats subjected to global cerebral ischemia secondary to cardiac arrest, neuronal death and post-ischemic myoclonus and seizures were significantly reduced by the ketogenic diet (Tai and Truong 2007; Tai et al., 2008). 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., 2006b).

3.2. Neuroprotective mechanisms of the ketogenic diet

The ketogenic diet has been associated with antioxidant effects in several studies (Fig. 2). First, mitochondria from animals fed a ketogenic diet produced lower amounts of ROS in isolated mitochondria (Sullivan et al., 2004b). Second, the ketogenic diet increased glutathione levels and glutathione peroxidase activity in the hippocampus (Ziegler et al., 2003; Jarrett et al., 2008). Third, the ketogenic diet increased UCP expression and activity in the hippocampus, thereby decreasing mitochondrial membrane potential and, as a result, diminishing the production of ROS (Sullivan et al., 2004b). The ketogenic diet also stimulated mitochondrial biogenesis and increased cerebral ATP and phosphocreatine concentrations, suggesting increased metabolic efficiency (DeVivo et al., 1978; Bough et al., 2006). Furthermore, genes encoding bioenergetic enzymes are up-regulated by the ketogenic diet (Noh et al., 2004; Bough et al., 2006). The combination of these mechanisms suggests that, as with calorie restriction, mitochondria are an important target of ketogenic diet action and that the resultant improvement in mitochondrial function (i.e.

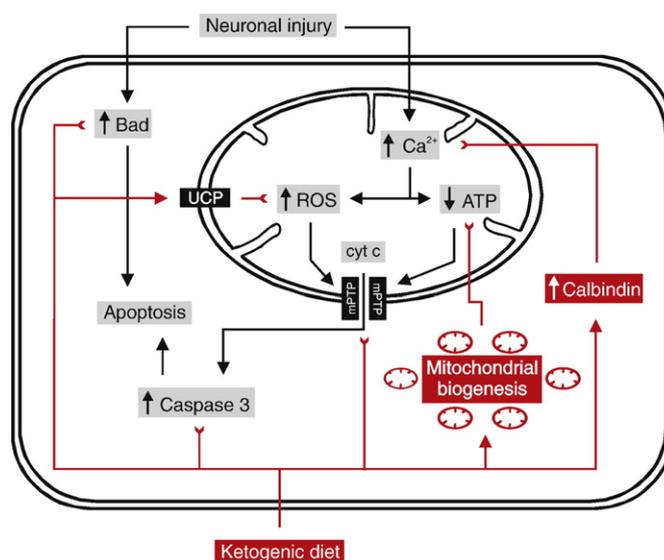


Fig. 2 – Mechanisms underlying the neuroprotective effects of the ketogenic diet. High levels of mitochondrial calcium following neuronal injury lead to increased mitochondrial production of reactive oxygen species (ROS), decreased synthesis of ATP and secondary opening of the mitochondrial permeability transition pore (mPTP). As a result, cytochrome c (cyt c) is released into the cytoplasm and initiates the apoptotic cascade. The ketogenic diet (KD) limits neuronal injury and death by stimulating the intracellular calcium buffer calbindin, promoting mitochondrial biogenesis (which increases ATP synthesis), and activating uncoupling proteins (which decreases ROS formation). Additionally, the KD inhibits apoptotic factors (Bad, caspase 3). Apoptotic pathways are depicted in black and neuroprotective pathways are shown in red. Dark arrows indicate excitatory effects whereas inverted arrows are inhibitory.

increased energy reserves combined with decreased production of ROS) could account for the ability of the diet to confer neuroprotection in models of neurological disease.

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 inhibits 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).

The anticonvulsant effects of ketogenic diet might further prevent brain damage by limiting seizure-induced neuronal hyperexcitability. In rodent brain, the ketogenic diet increases the levels of the inhibitory neurotransmitter γ -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). Consistently, the ketogenic diet has been associated with diminished transamination of glutamate to aspartate and increased decarboxylation of glutamate to GABA (Yudkoff et al., 2005). It remains unclear, however, whether the observed changes result in an anticonvulsant effect, particularly since GABA levels were elevated in non-seizure-prone areas of the brain (e.g., the superior colliculi and the cerebellum) and increases in GAD levels do not necessarily translate to increased GABA production (Rimvall and Martin 1992; Rimvall et al., 1993; Rimvall and Martin 1994). Nevertheless, stimulation of Schaffer collaterals in hippocampal slices of ketogenic diet-fed rats triggers fewer

population spikes than in slices from control animals, a process most probably mediated by enhanced GABA inhibition (Bough et al., 2003).

Additional mechanisms by which the ketogenic diet might limit neuronal hyperexcitability involve purinergic and noreadrenergic signaling. First, Masino and Geiger (2008) have proposed that, by enhancing ATP production, the ketogenic diet ultimately increases adenosine levels. Adenosine A_1 receptor activation subsequently decreases glutamate release and hyperpolarizes neurons. Second, blocking the synthesis of norepinephrine (by knocking out the gene for dopamine β -hydroxylase) eliminates the anticonvulsant effect of the ketogenic diet, whereas elevating synaptic levels of that neurotransmitter (by knocking out the norepinephrine transporter) potentiates the anticonvulsant effect (Szot et al., 2001; Martillotti et al., 2006). However, the contribution of norepinephrine to the neuroprotective effects of the ketogenic diet has yet to be confirmed. In fact, it should be emphasized that none of the anticonvulsant properties of the ketogenic diet have been shown to be neuroprotective, but such an association is conceivable based on the hypothesis that controlling seizures prevents excitotoxic injury.

4. Ketone bodies

Despite mounting evidence supporting the anticonvulsant and neuroprotective effects of ketogenic diets, the difficulty of adhering to a restrictive diet and the risk of systemic complications such as growth retardation, nephrolithiasis

and hyperlipidemia preclude more widespread implementation (Kwiterovich et al., 2003; Kang et al., 2004; Hartman and Vining 2007). Therefore, investigators have sought a safer, yet efficacious alternative. Within this context, ketone bodies have become the subject of growing interest and research. Under conditions of reduced glucose availability such as fasting, 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 consumption of a 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 constitutes an additional means of increasing ketone body synthesis and is not associated with any functional deficits.

4.1. Neuroprotective effects of ketone bodies

Similar to calorie restriction and to the ketogenic diet, ketones exhibit both anticonvulsant and neuroprotective properties. Acetoacetate and acetone exert anticonvulsant effects *in vivo*, but not β -hydroxybutyrate. Both acetoacetate and acetone decrease the incidence of seizures triggered by loud auditory stimuli in Frings audiogenic-susceptible mice (Rho et al., 2002). Acetone also suppresses seizures induced by amygdala kindling, by maximal electroshock and by the epileptogenic compounds pentylentetrazole, AY-9944 (a cholesterol synthesis inhibitor) and 4-aminopyridine (Likhodii et al., 2003; Hartman et al., 2007).

In animal models of Parkinson's disease, chronic subcutaneous infusion of β -hydroxybutyrate in mice confers partial protection against dopaminergic cell loss and motor deficits induced by the mitochondrial complex I inhibitor MPTP (Tieu et al., 2003). β -hydroxybutyrate also protects 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 correlates with blood levels of β -hydroxybutyrate (Reger et al., 2004). Furthermore, direct application of β -hydroxybutyrate protects cultured hippocampal neurons against $A\beta$ toxicity (Kashiwaya et al., 2000). Finally, exogenous administration of either β -hydroxybutyrate or acetoacetate reduces neuronal loss and improves 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 have been 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 ROS 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 (mPT) 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) increases 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., 2007). Increased survival is associated with the inhibition of electrophysiological signs of neuronal injury, specifically an irreversible depolarization associated with a significant decrease in membrane resistance. Acetoacetate (also in millimolar concentrations) has a similar effect in primary hippocampal cultures (Noh et al., 2006a). In addition, the combination of β -hydroxybutyrate and acetoacetate prevents oxidative impairment of long-term potentiation in the CA1 region of the hippocampus, indicating that ketone bodies not only limit neuronal loss but also preserve synaptic function (Maalouf and Rho, *in press*).

4.2. Neuroprotective mechanisms of ketone bodies

Although certain ketone bodies exhibit anticonvulsant properties, they do not affect neuronal excitability or synaptic transmission in the hippocampus (Erecinska et al., 1996; Thio et al., 2000). Millimolar concentrations of β -hydroxybutyrate and acetoacetate reduce, however, the spontaneous firing of neurons in the substantia nigra pars reticulata, another subcortical structure that may be critically involved in modulation of seizure activity (Ma et al., 2007). This effect requires the opening of ATP-sensitive potassium (K_{ATP}) channels, but its significance remains unclear because ketone bodies are known to raise ATP levels, which would shut down K_{ATP} channels.

In contrast to the ambiguous effects of ketone bodies on neuronal excitability, their antioxidant and metabolic properties have been consistently demonstrated (Fig. 3). A combination of β -hydroxybutyrate and acetoacetate (1 mM each) decreases the production of ROS by complex I of the mitochondrial respiratory chain (Maalouf et al., 2007). Specifically, in acutely isolated rat neocortical neurons, pretreatment with ketone bodies inhibits increases in intracellular levels of superoxide following prolonged exposure to glutamate. Ketone bodies also decrease ROS 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 ROS (Noh et al., 2006a).

In the study by Maalouf et al. (2007), 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,

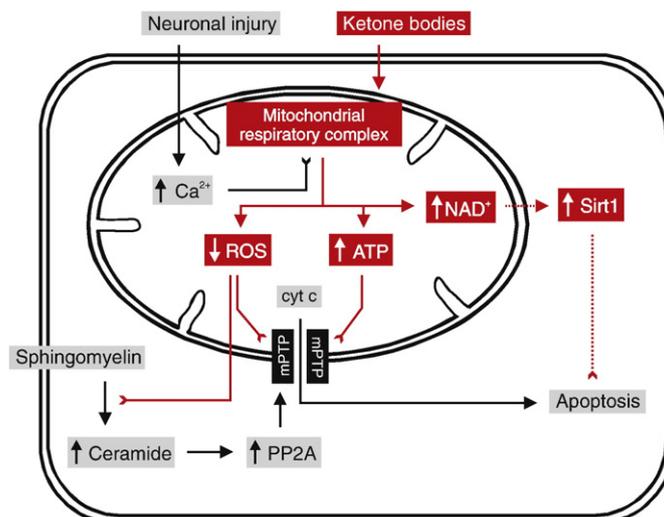


Fig. 3 – Mechanisms underlying the neuroprotective effects of ketone bodies. Neuronal injury increases mitochondrial calcium levels and inhibits mitochondrial respiration. As a result, production of reactive oxygen species (ROS) increases and ATP synthesis decreases, thereby facilitating the opening of the mitochondrial permeability transition pore (mPTP) and the activation of the apoptotic cascade by cytochrome c (cyt c). Concurrently, increased ROS levels enhance the conversion of sphingomyelin to ceramide and activate protein phosphatase 2A (PP2A), an apoptotic enzyme that can activate the mPTP. Ketone bodies improve mitochondrial respiration and, consequently, increase NAD^+ levels relative to NADH, decrease reactive oxygen species (ROS) formation and enhance ATP production. Ketone bodies also decrease PP2A activity by inhibiting the ROS-dependent conversion of sphingomyelin to ceramide. Sirt1 involvement (dotted lines) has not been substantiated, but this is highly likely given the increased NAD^+ to NADH ratio. Apoptotic pathways are depicted in black and neuroprotective pathways are shown in red. Dark arrows indicate excitatory effects whereas inverted arrows are inhibitory.

but not succinate. Given that NADH oxidation correlates with decreased mitochondrial formation of ROS (Duchen, 1992; Kudin et al., 2004; Sullivan et al., 2004a) and that pyruvate and malate drive mitochondrial respiration through complex I, the source of ROS in neurons (Turrens 2003), these findings strongly suggest that ketone bodies decrease the production of ROS 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 increases ATP production substantially in isolated brain mitochondria and in brain homogenates (Suzuki et al., 2001; Tieu et al., 2003). Similarly, acetoacetate increases phosphocreatine levels in cardiac myocytes (Squires 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 (Veech et al., 2001; Veech 2004). Moreover, these findings, which suggest that ketone bodies and the ketogenic diet enhance mitochondrial function through similar mechanisms, might explain why the ketogenic diet is helpful in patients with respiratory chain complex defects (Kang et al., 2006). The ketogenic diet and ketone bodies might either improve the function of the impaired mitochondria or, as suggested by Santra et al. (2004), allow healthy mitochondria to compensate for the deleterious effects of the defective ones.

In addition to the antioxidant and metabolic properties of ketone bodies, available data suggest that anti-apoptotic

mechanisms might be involved. Ketone bodies prevent neuronal injury and death caused by hydrogen peroxide or by the thiol oxidant and mPT activator, diamide (Kim et al., 2007). Inhibitors of mPT replicate the neuroprotective effects of ketone bodies. In addition, ketone bodies elevate the threshold for calcium-induced mPT in isolated brain mitochondria. Mitochondrial permeability transition can be triggered by various pathological mechanisms, 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).

Consistent with an anti-apoptotic effect, ketone bodies block the activation of protein phosphatase 2A by oxidative stress (Maalouf and Rho, in press). Protein phosphatase 2A is a serine-threonine protease 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 cytoplasmic membrane constituent, to ceramide in a series of biochemical reactions facilitated by ROS and inhibited by antioxidants such as glutathione (Zabrocki et al., 2002; Sultan et al., 2006; Won and Singh 2006). In turn, ceramide activates protein phosphatase 2A, inducing Bcl-2 dephosphorylation and cytochrome c release from mitochondria (Richter and Ghafourifar 1999; Ruvolo et al., 1999, 2002). In addition to triggering apoptosis, activation of protein phosphatase 2A, either by oxidative stress or

directly by ceramide analogues, inhibits LTP (Fukunaga et al., 2000; Kang-Park et al., 2003). Ketone bodies prevent the impairment of LTP by oxidative stress and ceramide and this effect is associated with the reduction of protein phosphatase 2A activity (Maalouf and Rho, *in press*).

In summary, current data suggest that mitochondria are the main target of ketone bodies. Improving mitochondrial function presents several obvious advantages. First, oxidative stress decreases. Second, ATP synthesis increases. Third, opening of permeability transition pore and the ensuing apoptotic cascade are inhibited. Increasing the NAD⁺/NADH ratio potentially provides an additional advantage, the activation of Sirt1, which, in turn, inhibits several apoptotic and inflammatory factors and promotes mitochondrial biogenesis. Ongoing studies are attempting to determine whether ketone bodies affect sirtuin activity.

5. Comparison of the neuroprotective properties of calorie restriction, of the ketogenic diet and of ketone bodies

Our review of the cellular and molecular mechanisms associated with calorie restriction, the ketogenic diet ketone bodies has identified several similarities between these

neuroprotective interventions, most importantly the prevention of disease related-mitochondrial dysfunction. Another similarity is the inhibition of apoptosis, although the specific mechanisms underlying the anti-apoptotic effects of each intervention might differ amongst the interventions discussed. Interestingly, recent findings indicate that calorie restriction, the ketogenic diet and ketone bodies exhibit anti-neoplastic properties as well (Seyfried et al., 2003; Mavropoulos et al., 2006; Hurstings et al., 2007; Zhou et al., 2007). Although prevention of carcinogenesis probably occurs independently of neuroprotection, elucidation of the underlying mechanisms might provide valuable insights into the neuroprotective aspects of either calorie restriction, the ketogenic diet or ketone bodies. For instance, Seyfried and Mukherjee (2005) have suggested that, unlike normal cells that can oxidize glucose as well as ketone bodies for energy, neoplastic cells are largely dependent on glucose. Therefore, the metabolic environment created by calorie restriction and by the ketogenic diet – decreased glucose and increased ketone bodies – is detrimental to neoplastic cells. The critical role of ketone bodies is further highlighted by preliminary data indicating that a combination of β -hydroxybutyrate and acetoacetate inhibits the growth of glioblastoma cells maintained in physiological concentrations of glucose (Marthaler et al., 2006).

Table 1 – Summary of the similarities and differences between calorie restriction, the ketogenic diet and ketone bodies

	Calorie restriction	Ketogenic diet	Ketone bodies
<i>Metabolic characteristics</i>			
Glucose level	Normal ^a	Normal ^a	Unknown ^b
Cholesterol and fatty acid levels	Normal	Increased	Unknown ^b
Ketone body levels	Variable ^c	Increased	Increased
<i>Neuroprotective mechanisms</i>			
Production of reactive oxygen species	Decreased	Decreased	Decreased
Antioxidant defenses	Possibly increased ^d	Increased	Normal
Synthesis of ATP	Relatively increased ^e	Increased	Increased
Sirtuin activity	Increased	Unknown	Unknown
Apoptotic factor activity	Decreased	Decreased	Probably decreased ^f
Neurotrophic factor activity	Variable ^g	Unknown	Unknown
Protein chaperone activity	Increased ^h	Decreased	Unknown
Inflammatory factor activity	Decreased ⁱ	Unknown	Unknown
Neurogenesis	Increased	Unknown	Unknown

Although many cellular and molecular mechanisms have been associated with calorie restriction, it has not been established which of these mechanisms underlies the neuroprotective effects of the diet. In contrast, less is known about the molecular mechanisms associated with ketone bodies. Available data suggests however that ketone bodies, similarly to calorie restriction and to the ketogenic diet, improve mitochondrial function, leading to decreased production of reactive oxygen species and increased (or at least maintained) ATP synthesis.

^a Glucose levels are lower on average in calorie restricted and ketogenic diet treated individuals than in those eating *ad libitum* but remain within normal limits despite a decreased intake of carbohydrates.

^b Only a few studies have tested ketone bodies *in vivo* to date and, as a consequence, the effects of ketone body administration on glucose and lipid levels remain unknown.

^c Intermittent fasting raises ketone body levels but ketosis is interrupted during periods of food intake.

^d Some studies have suggested that calorie restriction enhances antioxidant enzyme activity whereas others did not find any significant effects.

^e Measurements in mitochondria isolated from calorie restricted animals suggest a decrease in ATP production but ATP synthesis in intact cells and *in vivo* has been reported as normal, despite the decrease in calorie intake.

^f Although ketone bodies have not been shown to affect apoptotic factors directly, inhibition of protein phosphatase 2A activation and of mitochondrial permeability transition pore opening is consistent with an anti-apoptotic effect.

^g Calorie restriction increases the expression of the nerve growth factors BDNF, NT-3 and GDNF but decreases IGF-1 levels.

^h Although most studies reported an increase in protein chaperone activity following calorie restriction, one particular study (Park and Prolla 2005) suggested that calorie restriction decreases the expression of genes encoding heat shock proteins.

ⁱ Calorie restriction increases IFN γ activity in contrast to its overall anti-inflammatory effect.

Despite various similarities between calorie restriction, the ketogenic diet and ketone bodies, several differences exist (Table 1). When Bough et al. (2003) compared the antiepileptic effects of calorie restriction and of the ketogenic diet in the maximal dentate activation (MDA) protocol, they found that, although both diets significantly elevated MDA threshold and prolonged MDA latency compared with controls fed *ad libitum*, only the ketogenic diet slowed the prolongation of MDA duration. Similarly, the ketogenic diet was neuroprotective in animal models of familial ALS whereas calorie restriction accelerated disease progression (Pedersen and Mattson 1999; Zhao et al., 2006b).

From a metabolic standpoint, only the ketogenic diet increases brain and serum levels of polyunsaturated fatty acids (e.g., docosahexaenoic acid) that exhibit anticonvulsant and neuroprotective properties (Fraser et al., 2003; Taha et al., 2005; Bazan 2007). Polyunsaturated fatty acids and cerebrospinal fluid from children treated with the ketogenic diet appear to activate voltage-gated Shaker potassium channels expressed in *Xenopus* oocytes (Xu et al., 2008). Polyunsaturated fatty acids also 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). It is interesting to note, however, that ketone bodies are products of fatty acid catabolism and can therefore mediate some of neuroprotective effects of polyunsaturated fatty acids. Finally, Noh et al. (2004) reported that the ketogenic diet decreases the expression of heat shock proteins whereas all but one study involving calorie restriction described an increase in brain levels of heat shock proteins and other chaperones.

6. Concluding remarks

Calorie restriction and the ketogenic diet share two metabolic characteristics: reduced carbohydrate intake and a compensatory rise in ketone bodies. The neuroprotective effects of reduced carbohydrates *per se* are being investigated by several research groups (Mattson et al., 2003; Ingram et al., 2006). In this review, we have examined the possibility that ketone bodies might replicate some of the neuroprotective properties of calorie restriction and of the ketogenic diet. In support of this hypothesis, an expanding body of evidence indicates that ketone bodies are indeed neuroprotective. Moreover, the underlying mechanisms appear similar to those associated with calorie restriction and the ketogenic diet at the mitochondrial level. However, several important questions remain unanswered. First, the effects of ketone bodies on gene expression have not been investigated. Second, the neuroprotective effects of ketone bodies *in vivo* have not been thoroughly examined. It is imperative to demonstrate that the neuroprotective effects of ketone bodies prevent disease-related impairment of clinically relevant functions such as cognition. Future research will attempt to answer these critical questions and further our understanding of the mechanisms underlying calorie restriction, the ketogenic diet and ketone bodies.

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REFERENCES

- Abrous, D.N., Koehl, M., Le Moal, M., 2005. Adult neurogenesis: from precursors to network and physiology. *Physiol. Rev.* 85, 523–569.
- Agarwal, S., Sharma, S., Agarwal, V., Roy, N., 2005. Caloric restriction augments ROS defense in *S. cerevisiae*, by a Sir2p independent mechanism. *Free Radic. Res.* 39, 55–62.
- Agorogiannis, E.I., Agorogiannis, G.I., Papadimitriou, A., Hadjigeorgiou, G.M., 2004. Protein misfolding in neurodegenerative diseases. *Neuropathol. Appl. Neurobiol.* 30, 215–224.
- Aimone, J.B., Wiles, J., Gage, F.H., 2006. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat. Neurosci.* 9, 723–727.
- Anderson, R.M., Bitterman, K.J., Wood, J.G., Medvedik, O., Cohen, H., Lin, S.S., Manchester, J.K., Gordon, J.I., Sinclair, D.A., 2002. Manipulation of a nuclear NAD⁺ salvage pathway delays aging without altering steady-state NAD⁺ levels. *J. Biol. Chem.* 277, 18881–18890.
- Anderson, R.M., Bitterman, K.J., Wood, J.G., Medvedik, O., Sinclair, D.A., 2003. Nicotinamide and PNC1 govern lifespan extension by calorie restriction in *Saccharomyces cerevisiae*. *Nature* 423, 181–185.
- Andrews, Z.B., Diano, S., Horvath, T.L., 2005. Mitochondrial uncoupling proteins in the CNS: in support of function and survival. *Nat. Rev. Neurosci.* 6, 829–840.
- Andrews, Z.B., Rivera, A., Elsworth, J.D., Roth, R.H., Agnati, L., Gago, B., Abizaid, A., Schwartz, M., Fuxe, K., Horvath, T.L., 2006. Uncoupling protein-2 promotes nigrostriatal dopamine neuronal function. *Eur. J. Neurosci.* 24, 32–36.
- Anekonda, T.S., 2006. Resveratrol — a boon for treating Alzheimer's disease? *Brain Res. Rev.* 52, 316–326.
- Anekonda, T.S., Reddy, P.H., 2006. Neuronal protection by sirtuins in Alzheimer's disease. *J. Neurochem.* 96, 305–313.
- Araki, T., Sasaki, Y., Milbrandt, J., 2004. Increased nuclear NAD biosynthesis and SIRT1 activation prevent axonal degeneration. *Science* 305, 1010–1013.
- Auluck, P.K., Chan, H.Y., Trojanowski, J.Q., Lee, V.M., Bonini, N.M., 2002. Chaperone suppression of alpha-synuclein toxicity in a *Drosophila* model for Parkinson's disease. *Science* 295, 865–868.
- Baker, D.J., Betik, A.C., Krause, D.J., Hepple, R.T., 2006. No decline in skeletal muscle oxidative capacity with aging in long-term calorically restricted rats: effects are independent of mitochondrial DNA integrity. *J. Gerontol. A. Biol. Sci. Med. Sci.* 61, 675–684.
- Balaban, R.S., Nemoto, S., Finkel, T., 2005. Mitochondria, oxidants, and aging. *Cell* 120, 483–495.
- Barger, S.W., Horster, D., Furukawa, K., Goodman, Y., Krieglstein, J., Mattson, M.P., 1995. Tumor necrosis factors alpha and beta protect neurons against amyloid beta-peptide toxicity: evidence for involvement of a kappa B-binding factor and attenuation of peroxide and Ca²⁺ accumulation. *Proc. Natl. Acad. Sci. U. S. A.* 92, 9328–9332.
- Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A., 2006. Resveratrol

- improves health and survival of mice on a high-calorie diet. *Nature* 444, 337–342.
- Bazan, N.G., 2007. Omega-3 fatty acids, pro-inflammatory signaling and neuroprotection. *Curr. Opin. Clin. Nutr. Metab. Care* 10, 136–141.
- Bellush, L.L., Wright, A.M., Walker, J.P., Kopchick, J., Colvin, R.A., 1996. Caloric restriction and spatial learning in old mice. *Physiol. Behav.* 60, 541–547.
- Bernal, G.M., Peterson, D.A., 2004. Neural stem cells as therapeutic agents for age-related brain repair. *Aging Cell* 3, 345–351.
- Bevilacqua, L., Ramsey, J.J., Hagopian, K., Weindruch, R., Harper, M.E., 2005. Long-term caloric restriction increases UCP3 content but decreases proton leak and reactive oxygen species production in rat skeletal muscle mitochondria. *Am. J. Physiol. Endocrinol. Metab.* 289, E429–E438.
- Bhattacharya, A., Chandrasekar, B., Rahman, M.M., Banu, J., Kang, J.X., Fernandes, G., 2006. Inhibition of inflammatory response in transgenic fat-1 mice on a calorie-restricted diet. *Biochem. Biophys. Res. Commun.* 349, 925–930.
- Bitterman, K.J., Medvedik, O., Sinclair, D.A., 2003. Longevity regulation in *Saccharomyces cerevisiae*: linking metabolism, genome stability, and heterochromatin. *Microbiol. Mol. Biol. Rev.* 67, 376–399 (table of contents).
- Bondolfi, L., Ermini, F., Long, J.M., Ingram, D.K., Jucker, M., 2004. Impact of age and caloric restriction on neurogenesis in the dentate gyrus of C57BL/6 mice. *Neurobiol. Aging* 25, 333–340.
- Bordet, R., Ouk, T., Petraut, O., Gelé, P., Gautier, S., Laprais, M., Deplanque, D., Duriez, P., Staels, B., Fruchart, J.C., Bastide, M., 2006. PPAR: a new pharmacological target for neuroprotection in stroke and neurodegenerative diseases. *Biochem. Soc. Trans.* 34, 1341–1346.
- Bordone, L., Guarente, L., 2005. Calorie restriction, SIRT1 and metabolism: understanding longevity. *Nat. Rev. Mol. Cell Biol.* 6, 298–305.
- Bordone, L., Motta, M.C., Picard, F., Robinson, A., Jhala, U.S., Apfeld, J., McDonagh, T., Lemieux, M., McBurney, M., Szilvasi, A., Easlon, E.J., Lin, S.J., Guarente, L., 2006. Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic beta cells. *PLoS Biol.* 4, e31.
- Bough, K.J., Eagles, D.A., 1999. A ketogenic diet increases the resistance to pentylenetetrazole-induced seizures in the rat. *Epilepsia* 40, 138–143.
- Bough, K.J., Gudi, K., Han, F.T., Rathod, A.H., Eagles, D.A., 2002. An anticonvulsant profile of the ketogenic diet in the rat. *Epilepsy Res.* 50, 313–325.
- Bough, K.J., Rho, J.M., 2007. Anticonvulsant mechanisms of the ketogenic diet. *Epilepsia* 48, 43–58.
- Bough, K.J., Schwartzkroin, P.A., Rho, J.M., 2003. Calorie restriction and ketogenic diet diminish neuronal excitability in rat dentate gyrus in vivo. *Epilepsia* 44, 752–760.
- Bough, K.J., Wetherington, J., Hassel, B., Pare, J.F., Gawryluk, J.W., Grene, J.G., Shaw, R., Smith, Y., Geiger, J.D., Dingledine, R.J., 2006. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann. Neurol.* 60, 223–235.
- Bramham, C.R., Messaoudi, E., 2005. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog. Neurobiol.* 76, 99–125.
- Bramlett, H.M., Dietrich, W.D., 2004. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. *J. Cereb. Blood. Flow Metab.* 24, 133–150.
- Breidert, T., Callebert, J., Heneka, M.T., Landreth, G., Launay, J.M., Hirsch, E.C., 2002. Protective action of the peroxisome proliferator-activated receptor-gamma agonist pioglitazone in a mouse model of Parkinson's disease. *J. Neurochem.* 82, 615–624.
- Bruce-Keller, A.J., Umberger, G., McFall, R., Mattson, M.P., 1999. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Ann. Neurol.* 45, 8–15.
- Brunet, A., Sweeney, L.B., Sturgill, J.F., Chua, K.F., Greer, P.L., Lin, Y., Tran, H., Ross, S.E., Mostoslavsky, R., Cohen, H.Y., Hu, L.S., Cheng, H.L., Jedrychowski, M.P., Gygi, S.P., Sinclair, D.A., Alt, F.W., Greenberg, M.E., 2004. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science* 303, 2011–2015.
- Calabrese, E.J., Bachmann, K.A., Bailer, A.J., Bolger, P.M., Borak, J., Cai, L., Cedergreen, N., Cherian, M.G., Chiueh, C.C., Clarkson, T.W., Cook, R.R., Diamond, D.M., Doolittle, D.J., Dorato, M.A., Duke, S.O., Feinendegen, L., Gardner, D.E., Hart, R.W., Hastings, K.L., Hayes, A.W., Hoffmann, G.R., Ives, J.A., Jaworowski, Z., Johnson, T.E., Jonas, W.B., Kaminski, N.E., Keller, J.G., Klaunig, J.E., Knudsen, T.B., Kozumbo, W.J., Lettieri, T., Liu, S.Z., Maisseu, A., Maynard, K.I., Masoro, E.J., McClellan, R.O., Mehendale, H.M., Mothersill, C., Newlin, D.B., Nigg, H.N., Oehme, F.W., Phalen, R.F., Philbert, M.A., Rattan, S.I., Riviere, J.E., Rodricks, J., Sapolsky, R.M., Scott, B.R., Seymour, C., Sinclair, D.A., Smith-Sonneborn, J., Snow, E.T., Spear, L., Stevenson, D.E., Thomas, Y., Tubiana, M., Williams, G.M., Mattson, M.P., 2007. Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework. *Toxicol. Appl. Pharmacol.* 222, 122–128.
- Calabrese, V., Scapagnini, G., Giuffrida Stella, A.M., Bates, T.E., Clark, J.B., 2001. Mitochondrial involvement in brain function and dysfunction: relevance to aging, neurodegenerative disorders and longevity. *Neurochem. Res.* 26, 739–764.
- Caldeira da Silva, C.C., Cerqueira, F.M., Barbosa, L.F., Medeiros, M.H., Kowaltowski, A.J., in press. Mild mitochondrial uncoupling in mice affects energy metabolism, redox balance and longevity. *Aging Cell*.
- Canevari, L., Abramov, A.Y., Duchon, M.R., 2004. Toxicity of amyloid beta peptide: tales of calcium, mitochondria, and oxidative stress. *Neurochem. Res.* 29, 637–650.
- Caraballo, R.H., Cersósimo, R.O., Sakr, D., Cresta, A., Escobal, N., Fejerman, N., 2006. Ketogenic diet in patients with myoclonic–astatic epilepsy. *Epileptic Disord.* 8, 151–155.
- Chan, H.Y., Warrick, J.M., Gray-Board, G.L., Paulson, H.L., Donini, N.M., 2000. Mechanisms of chaperone suppression of polyglutamine disease: selectivity, synergy and modulation of protein solubility in *Drosophila*. *Hum. Mol. Genet.* 9, 2811–2820.
- Chaudhuri, T.K., Paul, S., 2006. Protein-misfolding diseases and chaperone-based therapeutic approaches. *Febs. J.* 273, 1331–1349.
- Cheng, B., Mattson, M.P., 1992. IGF-I and IGF-II protect cultured hippocampal and septal neurons against calcium-mediated hypoglycemic damage. *J. Neurosci.* 12, 1558–1566.
- Cheng, C.M., Hicks, K., Wang, J., Eagles, D.A., Bondy, C.A., 2004. Caloric restriction augments brain glutamic acid decarboxylase-65 and -67 expression. *J. Neurosci. Res.* 77, 270–276.
- Chua, K.F., Mostoslavsky, R., Lombard, D.B., Pang, W.W., Saito, S., Franco, S., Kaushal, D., Cheng, H.L., Fischer, M.R., Stokes, N., Murphy, M.M., Appella, E., Alt, F.W., 2005. Mammalian SIRT1 limits replicative life span in response to chronic genotoxic stress. *Cell Metab.* 2, 67–76.
- Chung, H.Y., Kim, H.J., Kim, K.W., Choi, J.S., Yu, B.P., 2002. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. *Microsc. Res. Tech.* 59, 264–272.
- Civitaresse, A.E., Carling, S., Heilbronn, L.K., Hulver, M.H., Ukropcova, B., Deutsch, W.A., Smith, S.R., Ravussin, E., CALERIE Pennington Team, 2007. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS Med.* 4, e76.
- Clément, K., Viguier, N., Piotou, C., Carette, C., Pelloux, V., Curat, C.A., Sicard, A., Rome, S., Benis, A., Zucker, J.D., Vidal, H., Laville, M., Barsh, G.S., Basdevant, A., Stich, V., Cancellou, R., Langin, D., 2004. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *Faseb. J.* 18, 1657–1669.

- Cohen, H.Y., Miller, C., Bitterman, K.J., Wall, N.R., Hekking, B., Kessler, B., Howitz, K.T., Gorospe, M., de Cabo, R., Sinclair, D.A., 2004. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* 305, 390–392.
- Conti, B., Sanchez-Alavez, M., Winsky-Sommerer, R., Morale, M.C., Lucero, J., Brownell, S., Fabre, V., Huitron-Resendiz, S., Henriksen, S., Zorrilla, E.P., de Lecea, L., Bartfai, T., 2006. Transgenic mice with a reduced core body temperature have an increased life span. *Science* 314, 825–828.
- Conti, B., Sugama, S., Lucero, J., Winsky-Sommerer, R., Wirz, S.A., Maher, P., Andrews, Z., Barr, A.M., Morale, M.C., Panenda, C., Pemberton, J., Gaidarova, S., Behrens, M.M., Beal, F., Sanna, P.P., Horvath, T., Bartfai, T., 2005. Uncoupling protein 2 protects dopaminergic neurons from acute 1,2,3,6-methyl-phenyl-tetrahydropyridine toxicity. *J. Neurochem.* 93, 493–501.
- Cullingford, T.E., 2004. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. *Prostaglandins Leukot. Essent. Fatty Acids* 70, 253–264.
- Cummings, C.J., Sun, Y., Opal, P., Antalffy, B., Mestril, R., Orr, H.T., Dillmann, W.H., Zoghbi, H.Y., 2001. Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice. *Hum. Mol. Genet.* 10, 1511–1518.
- Cunnane, S.C., Likhodii, S.S., 2004. Claims to identify detrimental effects of the ketogenic diet (KD) on cognitive function in rats. *Pediatr. Res.* 56, 663–664.
- Dagda, R.K., Zaucha, J.A., Wadzinski, B.E., Strack, S., 2003. A developmentally regulated, neuron-specific splice variant of the variable subunit Bbeta targets protein phosphatase 2A to mitochondria and modulates apoptosis. *J. Biol. Chem.* 278, 24976–24985.
- Dahlin, M., Elfving, A., Ungerstedt, U., Amark, P., 2005. The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy. *Epilepsy Res.* 64, 115–125.
- Davis, L.M., Pauly, J.R., Readnower, R.D., Rho, J.M., Sullivan, P.G., 2008. Fasting is neuroprotective following traumatic brain injury. *J. Neurosci. Res.* 2008 86, 1812–1822.
- Daynes, R.A., Jones, D.C., 2002. Emerging roles of PPARs in inflammation and immunity. *Nat. Rev. Immunol.* 2, 748–759.
- de la Monte, S.M., Wands, J.R., 2005. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J. Alzheimers Dis.* 7, 45–61.
- de Lau, L.M., Bornebroek, M., Witteman, J.C., Hofman, A., Koudstaal, P.J., Breteler, M.M., 2005. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology* 64, 2040–2045.
- Deruisseau, K.C., Kavazis, A.N., Judge, S., Murlasits, Z., Deering, M.A., Quindry, J.C., Lee, Y., Falk, D.J., Leeuwenburgh, C., Powers, S.K., 2006. Moderate caloric restriction increases diaphragmatic antioxidant enzyme mRNA, but not when combined with lifelong exercise. *Antioxid. Redox. Signal* 8, 539–547.
- DeVivo, D.C., Leckie, M.P., Ferrendelli, J.S., McDougal Jr., D.B., 1978. Chronic ketosis and cerebral metabolism. *Ann. Neurol.* 3, 331–337.
- Diano, S., Matthews, R.T., Patrylo, P., Yang, L., Beal, M.F., Barnstable, C.J., Horvath, T.L., 2003. Uncoupling protein 2 prevents neuronal death including that occurring during seizures: a mechanism for preconditioning. *Endocrinology* 144, 5014–5021.
- Doré, S., Kar, S., Quirion, R., 1997. Insulin-like growth factor I protects and rescues hippocampal neurons against beta-amyloid- and human amylin-induced toxicity. *Proc. Natl. Acad. Sci. U. S. A.* 94, 4772–4777.
- Drew, B., Phaneuf, S., Dirks, A., Selman, C., Gredilla, R., Lezza, A., Barja, G., Leeuwenburgh, C., 2003. Effects of aging and caloric restriction on mitochondrial energy production in gastrocnemius muscle and heart. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284, R474–R480.
- Duan, W., Guo, Z., Jiang, H., Ware, M., Li, X.J., Mattson, M.P., 2003. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc. Natl. Acad. Sci. U. S. A.* 100, 2911–2916.
- Duan, W., Guo, Z., Mattson, M.P., 2001a. Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. *J. Neurochem.* 76, 619–626.
- Duan, W., Lee, J., Guo, Z., Mattson, M.P., 2001b. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. *J. Mol. Neurosci.* 16, 1–12.
- Duan, W., Mattson, M.P., 1999. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. *J. Neurosci. Res.* 57, 195–206.
- Duchen, M.R., 1992. Ca(2+)-dependent changes in the mitochondrial energetics in single dissociated mouse sensory neurons. *Biochem. J.* 283, 41–50.
- Eagles, D.A., Boyd, S.J., Kotak, A., Allan, F., 2003. Calorie restriction of a high-carbohydrate diet elevates the threshold of PTZ-induced seizures to values equal to those seen with a ketogenic diet. *Epilepsy Res.* 54, 41–52.
- Eckles-Smith, K., Clayton, D., Bickford, P., Browning, M.D., 2000. Caloric restriction prevents age-related deficits in LTP and in NMDA receptor expression. *Brain Res. Mol. Brain Res.* 78, 154–162.
- Ehrenfried, J.A., Evers, B.M., Chu, K.U., Townsend Jr., C.M., Thompson, J.C., 1996. Caloric restriction increases the expression of heat shock protein in the gut. *Ann. Surg.* 223, 592–597.
- Emerit, J., Edeas, M., Bricaire, F., 2004. Neurodegenerative diseases and oxidative stress. *Biomed. Pharmacother.* 58, 39–46.
- Erecinska, M., Nelson, D., Daikhin, Y., Yudkoff, M., 1996. Regulation of GABA level in rat brain synaptosomes: fluxes through enzymes of the GABA shunt and effects of glutamate, calcium and ketone bodies. *J. Neurochem.* 67, 2325–2334.
- Eun, S.H., Kang, H.C., Kim, D.W., Kim, H.D., 2006. Ketogenic diet for treatment of infantile spasms. *Brain Dev.* 28, 566–571.
- Evangeliou, A., Vlachonikolis, I., Mihailidou, H., Spilioti, M., Skarpalezou, A., Makaronas, N., Prokopiou, A., Christodoulou, P., Liapi-Adamidou, G., Helidonis, E., Sbyrakis, S., Smeitink, J., 2003. Application of a ketogenic diet in children with autistic behavior: pilot study. *J. Child Neurol.* 18, 113–118.
- Fabrizio, P., Gattazzo, C., Battistella, L., Wei, M., Cheng, C., McGrew, K., Longo, V.D., 2005. Sir2 blocks extreme life-span extension. *Cell* 123, 655–667.
- Fabrizio, P., Longo, V.D., 2003. The chronological life span of *Saccharomyces cerevisiae*. *Aging Cell* 2, 73–81.
- Feinstein, D.L., Galea, E., Gavrielyuk, V., Brosnan, C.F., Whitacre, C.C., Dumitrescu-Ozimek, L., Landreth, G.E., Pershadasingh, H.A., Weinberg, G., Heneka, M.T., 2002. Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis. *Ann. Neurol.* 51, 694–702.
- Fernyhough, P., Smith, D.R., Schapansky, J., Van Der Ploeg, R., Gardiner, N.J., Tweed, C.W., Kontos, A., Freeman, L., Purves-Tyson, T.D., Glazner, G.W., 2005. Activation of nuclear factor-kappaB via endogenous tumor necrosis factor alpha regulates survival of axotomized adult sensory neurons. *J. Neurosci.* 25, 1682–1690.
- Fraser, D.D., Whiting, S., Andrew, R.D., Macdonald, E.A., Musa-Veloso, K., Cunnane, S.C., 2003. Elevated polyunsaturated fatty acids in blood serum obtained from children on the ketogenic diet. *Neurology* 60, 1026–1029.
- Freeman, J., Veggiotti, P., Lanzi, G., Tagliabue, A., Perucca, E., Institute of Neurology IRCCS C. Mondino Foundation, 2006. The

- ketogenic diet: from molecular mechanisms to clinical effects. *Epilepsy Res.* 68, 145–180.
- Freeman, J.M., Vining, E.P., Pillas, D.J., Pyzik, P.L., Casey, J.C., Kelly, L.M., 1998. The efficacy of the ketogenic diet—1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 102, 1358–1363.
- Frier, B., Locke, M., 2005. Preservation of heat stress induced myocardial hsp 72 in aged animals following caloric restriction. *Exp. Gerontol.* 40, 615–617.
- Fukunaga, K., Muller, D., Ohmitsu, M., Bakó, E., DePaoli-Roach, A.A., Miyamoto, E., 2000. Decreased protein phosphatase 2A activity in hippocampal long-term potentiation. *J. Neurochem.* 74, 807–817.
- Furukawa-Hibi, Y., Kobayashi, Y., Chen, C., Motoyama, N., 2005. FOXO transcription factors in cell-cycle regulation and the response to oxidative stress. *Antioxid. Redox. Signal* 7, 752–760.
- Gallo, C.M., Smith Jr., D.L., Smith, J.S., 2004. Nicotinamide clearance by Pnc1 directly regulates Sir2-mediated silencing and longevity. *Mol. Cell Biol.* 24, 1301–1312.
- Garriga-Canut, M., Schoenike, B., Qazi, R., Bergendahl, K., Daley, T.J., Pfender, R.M., Morrison, J.F., Ockuly, J., Stafstrom, C., Sutula, T., Roopra, A., 2006. 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure. *Nat. Neurosci.* 9, 1382–1387.
- Gasior, M., Rogawski, M.A., Hartman, A.L., 2006. Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav. Pharmacol.* 17, 431–439.
- Giffard, R.G., Xu, L., Zhao, H., Carrico, W., Ouyang, Y., Qiao, Y., Sapolsky, R., Steinberg, G., Hu, B., Yenari, M.A., 2004. Chaperones, protein aggregation, and brain protection from hypoxic/ischemic injury. *J. Exp. Biol.* 207, 3213–3220.
- Gloire, G., Legrand-Poels, S., Piette, J., 2006. NF-kappaB activation by reactive oxygen species: fifteen years later. *Biochem. Pharmacol.* 72, 1493–1505.
- Gong, X., Shang, F., Obin, M., Palmer, H., Scrofano, M.M., Jahngen-Hodge, J., Smith, D.E., Taylor, A., 1997. Antioxidant enzyme activities in lens, liver and kidney of calorie restricted Emory mice. *Mech. Ageing Dev.* 99, 181–192.
- Gonzales-Pacheco, D.M., Buss, W.C., Koehler, K.M., Woodside, W.F., Alpert, S.S., 1993. Energy restriction reduces metabolic rate in adult male Fisher-344 rats. *J. Nutr.* 123, 90–97.
- Gredilla, R., Barja, G., 2005. Minireview: the role of oxidative stress in relation to caloric restriction and longevity. *Endocrinology* 146, 3713–3717.
- Gredilla, R., Sanz, A., Lopez-Torres, M., Barja, G., 2001. Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart. *Faseb. J.* 15, 1589–1591.
- Green, D.R., Kroemer, G., 2004. The pathophysiology of mitochondrial cell death. *Science* 305, 626–629.
- Greene, A.E., Todorova, M.T., McGowan, R., Syefried, T.N., 2001. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. *Epilepsia* 42, 1371–1378.
- Greene, A.E., Todorova, M.T., Seyfried, T.N., 2003. Perspectives on the metabolic management of epilepsy through dietary reduction of glucose and elevation of ketone bodies. *J. Neurochem.* 86, 529–537.
- Guarente, L., 2008. Mitochondria — a nexus for aging, calorie restriction, and sirtuins? *Cell* 132, 171–176.
- Guarente, L., Picard, F., 2005. Calorie restriction—the SIR2 connection. *Cell* 120, 473–482.
- Guo, Z., Ersoz, A., Butterfield, D.A., Mattson, M.P., 2000. Beneficial effects of dietary restriction on cerebral cortical synaptic terminals: preservation of glucose and glutamate transport and mitochondrial function after exposure to amyloid beta-peptide, iron, and 3-nitropropionic acid. *J. Neurochem.* 75, 314–320.
- Guzman, M., Blazquez, C., 2004. Ketone body synthesis in the brain: possible neuroprotective effects. *Prostaglandins Leukot. Essent. Fatty Acids* 70, 287–292.
- Halagappa, V.K., Guo, Z., Pearson, M., Matsuoka, Y., Cutler, R.G., LaFerla, F.M., Mattson, M.P., 2007. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol. Dis.* 26, 212–220.
- Hamanoue, M., Middleton, G., Wyatt, S., Jaffray, E., Hay, R.T., Davies, A.M., 1999. p75-mediated NF-kappaB activation enhances the survival response of developing sensory neurons to nerve growth factor. *Mol. Cell Neurosci.* 14, 28–40.
- Hansalik, M., Skalicky, M., Vidik, A., 2006. Impairment of water maze behaviour with ageing is counteracted by maze learning earlier in life but not by physical exercise, food restriction or housing conditions. *Exp. Gerontol.* 41, 169–174.
- Harper, M.E., Bevilacqua, L., Hagopian, K., Weindruch, R., Ramsey, J.J., 2004. Ageing, oxidative stress, and mitochondrial uncoupling. *Acta. Physiol. Scand.* 182, 321–331.
- Hartl, F.U., Hayer-Hartl, M., 2002. Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* 295, 1852–1858.
- Hartman, A.L., Gasior, M., Vining, E.P., Rogawski, M.A., 2007. The neuropharmacology of the ketogenic diet. *Pediatr. Neurol.* 36, 281–292.
- Hartman, A.L., Vining, E.P., 2007. Clinical aspects of the ketogenic diet. *Epilepsia* 48, 31–42.
- Hashimoto, T., Watanabe, S., 2005. Chronic food restriction enhances memory in mice—analysis with matched drive levels. *Neuroreport* 16, 1129–1133.
- Haymond, M.W., Karl, I.E., Clarke, W.L., Pagliara, A.S., Santiago, J.V., 1982. Differences in circulating gluconeogenic substrates during short-term fasting in men, women, and children. *Metabolism* 31, 33–42.
- He, X.P., Kotloski, R., Nef, S., Luikart, B.W., Parada, L.F., McNamara, J.O., 2004. Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. *Neuron* 43, 31–42.
- Heck, S., Lezoualc'h, F., Engert, S., Behl, C., 1999. Insulin-like growth factor-1-mediated neuroprotection against oxidative stress is associated with activation of nuclear factor kappaB. *J. Biol. Chem.* 274, 9828–9835.
- Heilbronn, L.K., de Jonge, L., Frisard, M.I., DeLany, J.P., Larson-Meyer, D.E., Rood, J., Nguyen, T., Martin, C.K., Volaufova, J., Most, M.M., Greenway, F.L., Smith, S.R., Deutsch, W.A., Williamson, D.A., Ravussin, E., Pennington CALERIE Team, 2006. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *Jama* 295, 1539–1548.
- Hemingway, C., Freeman, J.M., Pillas, D.J., Pyzik, P.L., 2001. The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. *Pediatrics* 108, 898–905.
- Heneka, M.T., Sastre, M., Dumitrescu-Ozimek, L., Hanke, A., Dewachter, I., Kuiperi, C., O'Banion, K., Klockgether, T., Van Leuven, F., Landreth, G.E., 2005. Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1–42 levels in APPV717I transgenic mice. *Brain* 128, 1442–1453.
- Hepple, R.T., Baker, D.J., Kaczor, J.J., Krause, D.J., 2005. Long-term caloric restriction abrogates the age-related decline in skeletal muscle aerobic function. *Faseb. J.* 19, 1320–1322.
- Heydari, A.R., Conrad, C.C., Richardson, A., 1995. Expression of heat shock genes in hepatocytes is affected by age and food restriction in rats. *J. Nutr.* 125, 410–418.
- Hisahara, S., Chiba, S., Matsumoto, H., Horio, Y., 2005. Transcriptional regulation of neuronal genes and its effect on neural functions: NAD-dependent histone deacetylase SIRT1 (Sir2alpha). *J. Pharmacol. Sci.* 98, 200–204.

- Hori, A., Tandon, P., Holmes, G.L., Stafstrom, C.E., 1997. Ketogenic diet: effects on expression of kindled seizures and behavior in adult rats. *Epilepsia* 38, 750–758.
- Hori, N., Hirotsu, I., Davis, P.J., Carpenter, D.O., 1992. Long-term potentiation is lost in aged rats but preserved by calorie restriction. *Neuroreport* 3, 1085–1088.
- Hu, X., Nesic-Taylor, O., Qiu, J., Rea, H.C., Fabian, R., Rassin, D.K., Perez-Polo, J.R., 2005. Activation of nuclear factor-kappaB signaling pathway by interleukin-1 after hypoxia/ischemia in neonatal rat hippocampus and cortex. *J. Neurochem.* 93, 26–37.
- Hunt, N.D., Hyun, D.H., Allard, J.S., Minor, R.K., Mattson, M.P., Ingram, D.K., de Cabo, R., 2006. Bioenergetics of aging and calorie restriction. *Ageing Res. Rev.* 5, 125–143.
- Hursting, S.D., Lashinger, L.M., Colbert, L.H., Rogers, C.J., Wheatley, K.W., Nunez, N.P., Mahabir, S., Barrett, J.C., Forman, M.R., Perkins, S.N., 2007. Energy balance and carcinogenesis: underlying pathways and targets for intervention. *Curr. Cancer Drug Targets* 7, 484–491.
- Imai, S., Armstrong, C.M., Kaerberlein, M., Guarente, L., 2000. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature* 403, 795–800.
- Imamura, K., Takeshima, T., Kashiwaya, Y., Nakaso, K., Nakashima, K., 2006. D-beta-hydroxybutyrate protects dopaminergic SH-SY5Y cells in a rotenone model of Parkinson's disease. *J. Neurosci. Res.* 84, 1376–1384.
- Ingram, D.K., Weindruch, R., Spangler, E.L., Freeman, J.R., Walford, R.L., 1987. Dietary restriction benefits learning and motor performance of aged mice. *J. Gerontol.* 42, 78–81.
- Ingram, D.K., Zhu, M., Mamczarz, J., Zou, S., Lane, M.A., Roth, G.S., deCabo, R., 2006. Calorie restriction mimetics: an emerging research field. *Ageing Cell* 5, 97–108.
- Jagust, W., Harvey, D., Mungas, D., Haan, M., 2005. Central obesity and the aging brain. *Arch. Neurol.* 62, 1545–1548.
- Jang, J.H., Surh, Y.J., 2003. Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death. *Free Radic. Biol. Med.* 34, 1100–1110.
- Janssens, V., Goris, J., 2001. Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. *Biochem. J.* 353, 417–439.
- Jarrett, S.G., Milder, J.B., Liang, L.P., Patel, M., 2008. The ketogenic diet increases mitochondrial glutathione levels. *J. Neurochem.* 106, 1044–1051.
- Johnson, J.B., Laub, D.R., John, S., 2006. The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life. *Med. Hypotheses* 67, 209–211.
- Kaerberlein, M., Kirkland, K.T., Fields, S., Kennedy, B.K., 2004. Sir2-independent life span extension by calorie restriction in yeast. *PLoS Biol.* 2, E296.
- Kaerberlein, M., McVey, M., Guarente, L., 1999. The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes Dev.* 13, 2570–2580.
- Kaerberlein, M., Powers III, R.W., Steffen, K.K., Westman, E.A., Hu, D., Dang, N., Kerr, E.O., Kirkland, K.T., Fields, S., Kennedy, B.K., 2005. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science* 310, 1193–1196.
- Kalani, R., Judge, S., Carter, C., Pahor, M., Leeuwenburgh, C., 2006. Effects of caloric restriction and exercise on age-related, chronic inflammation assessed by C-reactive protein and interleukin-6. *J. Gerontol. A. Biol. Sci. Med. Sci.* 61, 211–217.
- Kaltschmidt, B., Widera, D., Kaltschmidt, C., 2005. Signaling via NF-kappaB in the nervous system. *Biochim. Biophys. Acta.* 1745, 287–299.
- Kang-Park, M.H., Sarda, M.A., Jones, K.H., Moore, S.D., Schenolikar, S., Clark, S., Wilson, W.A., 2003. Protein phosphatases mediate depotentiation induced by high-intensity theta-burst stimulation. *J. Neurophysiol.* 89, 684–690.
- Kang, H.C., Chung, D.E., Kim, D.W., Kim, H.D., 2004. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia* 45, 1116–1123.
- Kang, H.C., Lee, Y.M., Kim, H.D., Lee, J.S., Slama, A., 2007. Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. *Epilepsia* 48, 82–88.
- Karin, M., 2006. Nuclear factor-kappaB in cancer development and progression. *Nature* 441, 431–436.
- Kashiwaya, Y., Takeshima, T., Mori, N., Nakashima, K., Clarke, K., Veech, R.L., 2000. D-beta-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. *Proc. Natl. Acad. Sci. U. S. A.* 97, 5440–5444.
- Keller, J.N., Schmitt, F.A., Scheff, S.W., Ding, Q., Chen, Q., Butterfield, D.A., Markesbery, W.R., 2005. Evidence of increased oxidative damage in subjects with mild cognitive impairment. *Neurology* 64, 1152–1156.
- Kiaei, M., Kipiani, K., Chen, J., Calingasan, N.Y., Beal, M.F., 2005. Peroxisome proliferator-activated receptor-gamma agonist extends survival in transgenic mouse model of amyotrophic lateral sclerosis. *Exp. Neurol.* 191, 331–336.
- Kim, H.J., Hwang, J.J., Behrens, M.M., Snider, B.J., Choi, D.W., Koh, J.Y., 2003. TrkB mediates BDNF-induced potentiation of neuronal necrosis in cortical culture. *Neurobiol. Dis.* 14, 110–119.
- Kim, S.H., Won, S.J., Sohn, S., Kwon, H.J., Lee, J.Y., Park, J.H., Gwag, B.J., 2002. Brain-derived neurotrophic factor can act as a proneurotrophic factor through transcriptional and translational activation of NADPH oxidase. *J. Cell Biol.* 159, 821–831.
- Kim, Y.J., Kim, H.J., No, J.K., Chung, H.Y., Fernandes, G., 2006. Anti-inflammatory action of dietary fish oil and calorie restriction. *Life Sci.* 78, 2523–2532.
- Kim do, Y., Davis, L.M., Sullivan, P.G., Maalouf, M., Simeone, T.A., van Brederode, J., Rho, J.M., 2007. Ketone bodies are protective against oxidative stress in neocortical neurons. *J. Neurochem.* 101, 1316–1326.
- King, V.R., Huang, W.L., Dyal, S.C., Curran, O.E., Priestley, J.V., Michael-Titus, A.T., 2006. Omega-3 fatty acids improve recovery, whereas omega-6 fatty acids worsen outcome, after spinal cord injury in the adult rat. *J. Neurosci.* 26, 4672–4680.
- Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kåreholt, I., Winblad, B., Helkala, E.L., Tuomilehto, J., Soininen, H., Nissinen, A., 2005. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch. Neurol.* 62, 1556–1560.
- Klepper, J., Scheffer, H., Leiendecker, B., Gertsen, E., Binder, S., Leferink, M., Hertzberg, C., Näke, A., Voit, T., Willemsen, M.A., 2005. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: a 2- to 5-year follow-up of 15 children enrolled prospectively. *Neuropediatrics* 36, 302–308.
- Kossoff, E.H., 2004. More fat and fewer seizures: dietary therapies for epilepsy. *Lancet Neurol.* 3, 415–420.
- Kossoff, E.H., Pyzik, P.L., McGrogan, J.R., Vining, E.P., Freeman, J.M., 2002. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics* 109, 780–783.
- Kowaltowski, A.J., Castilho, R.F., Vercesi, A.E., 2001. Mitochondrial permeability transition and oxidative stress. *FEBS Lett.* 495, 12–15.
- Krauss, S., Zhang, C.Y., Lowell, B.B., 2005. The mitochondrial uncoupling-protein homologues. *Nat. Rev. Mol. Cell Biol.* 6, 248–261.
- Kroemer, G., Galluzzi, L., Brenner, C., 2007. Mitochondrial membrane permeabilization in cell death. *Physiol. Rev.* 87, 99–163.
- Kudin, A.P., Bimpong-Buta, N.Y., Vielhaber, S., Elger, C.E., Kunz, W.S., 2004. Characterization of superoxide-producing sites in isolated brain mitochondria. *J. Biol. Chem.* 279, 4127–4135.
- Kume, S., Haneda, M., Kanasaki, K., Sugimoto, T., Araki, S., Isono, M., Ishiki, K., Uzu, T., Kashiwagi, A., Koya, D., 2006. Silent information regulator 2 (SIRT1) attenuates oxidative

- stress-induced mesangial cell apoptosis via p53 deacetylation. *Free Radic. Biol. Med.* 40, 2175–2182.
- Kwiterovich Jr., P.O., Vining, E.P., Pyzik, P., Skolasky Jr., R., Freeman, J.M., 2003. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. *Jama* 290, 912–920.
- Laffel, L., 1999. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab. Res. Rev.* 15, 412–426.
- Lambert, A.J., Merry, B.J., 2004. Effect of caloric restriction on mitochondrial reactive oxygen species production and bioenergetics: reversal by insulin. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 286, R71–R79.
- Lamers, K.J., Gabreëls, F.J., Renier, W.O., Wevers, R.A., Doesburg, W.H., 1995. Fasting studies in cerebrospinal fluid and blood in children with epilepsy of unknown origin. *Epilepsy Res.* 21, 59–63.
- Lamming, D.W., Latorre-Esteves, M., Medvedik, O., Wong, S.N., Tsang, F.A., Wang, C., Lin, S.J., Sinclair, D.A., 2005. HST2 mediates SIR2-independent life-span extension by calorie restriction. *Science* 309, 1861–1864.
- Lauritzen, I., Blondeau, N., Heurteaux, C., Widmann, C., Romey, G., Lazdunski, M., 2000. Polyunsaturated fatty acids are potent neuroprotectors. *EMBO J.* 19, 1784–1793.
- Lebrun, B., Bariohay, B., Moyses, E., Jean, A., 2006. Brain-derived neurotrophic factor (BDNF) and food intake regulation: a minireview. *Auton. Neurosci.* 126–127, 30–38.
- Lee, J., Auyeung, W.W., Mattson, M.P., 2003. Interactive effects of excitotoxic injury and dietary restriction on microgliosis and neurogenesis in the hippocampus of adult mice. *Neuromolecular Med.* 4, 179–196.
- Lee, J., Duan, W., Long, J.M., Ingram, D.K., Mattson, M.P., 2000. Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. *J. Mol. Neurosci.* 15, 99–108.
- Lee, J., Duan, W., Mattson, M.P., 2002a. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J. Neurochem.* 82, 1367–1375.
- Lee, J., Seroogy, K.B., Mattson, M.P., 2002b. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *J. Neurochem.* 80, 539–547.
- Lee, J., Kim, S.J., Son, T.G., Chan, S.L., Mattson, M.P., 2006. Interferon-gamma is up-regulated in the hippocampus in response to intermittent fasting and protects hippocampal neurons against excitotoxicity. *J. Neurosci. Res.* 83, 1552–1557.
- Lefevre, F., Aronson, N., 2000. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. *Pediatrics* 105, E46.
- Lichtenwalner, R.J., Forbes, M.E., Bennett, S.A., Lynch, C.D., Sonntag, W.E., Riddle, D.R., 2001. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. *Neuroscience* 107, 603–613.
- Likhodii, S.S., Serbanescu, I., Cortez, M.A., Murphy, P., Snead III, O.C., Burnham, W.M., 2003. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. *Ann. Neurol.* 54, 219–226.
- Lim, C.S., Potts, M., Helm, R.F., 2006. Nicotinamide extends the replicative life span of primary human cells. *Mech. Ageing Dev.* 127, 511–514.
- Lin, S.J., Defossez, P.A., Guarente, L., 2000. Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science* 289, 2126–2128.
- Lin, S.J., Ford, E., Haigis, M., Liszt, G., Guarente, L., 2004. Calorie restriction extends yeast life span by lowering the level of NADH. *Genes Dev.* 18, 12–16.
- Lin, S.J., Kaeberlein, M., Andalis, A.A., Sturtz, L.A., Defossez, P.A., Culotta, V.C., Fink, G.R., Guarente, L., 2002. Calorie restriction extends *Saccharomyces cerevisiae* lifespan by increasing respiration. *Nature* 418, 344–348.
- Liu, D., Chan, S.L., de Souza-Pinto, N.C., Slevin, J.R., Wersto, R.P., Zhan, M., Mustafa, K., de Cabo, R., Mattson, M.P., 2006. Mitochondrial UCP4 mediates an adaptive shift in energy metabolism and increases the resistance of neurons to metabolic and oxidative stress. *Neuromolecular Med.* 8, 389–414.
- Lledo, P.M., Alonso, M., Grubb, M.S., 2006. Adult neurogenesis and functional plasticity in neuronal circuits. *Nat. Rev. Neurosci.* 7, 179–193.
- Longo, V.D., Kennedy, B.K., 2006. Sirtuins in aging and age-related disease. *Cell* 126, 257–268.
- Lopez-Lluch, G., Hunt, N., Jones, B., Zhu, M., Jamieson, H., Hilmer, S., Cascajo, M.V., Allard, J., Ingram, D.K., Navas, P., de Cabo, R., 2006. Calorie restriction induces mitochondrial biogenesis and bioenergetic efficiency. *Proc. Natl. Acad. Sci. U. S. A.* 103, 1768–1773.
- Lopez-Torres, M., Gredilla, R., Sanz, A., Barja, G., 2002. Influence of aging and long-term caloric restriction on oxygen radical generation and oxidative DNA damage in rat liver mitochondria. *Free Radic. Biol. Med.* 32, 882–889.
- Lowenstein, D.H., Chan, P.H., Miles, M.F., 1991. The stress protein response in cultured neurons: characterization and evidence for a protective role in excitotoxicity. *Neuron* 7, 1053–1060.
- Luchsinger, J.A., Tang, M.X., Shea, S., Mayeux, R., 2002. Caloric intake and the risk of Alzheimer disease. *Arch. Neurol.* 59, 1258–1263.
- Luo, J., Nikolaev, A.Y., Imai, S., Chen, D., Su, F., Shiloh, A., Guarente, L., Gu, W., 2001. Negative control of p53 by Sir2alpha promotes cell survival under stress. *Cell* 107, 137–148.
- Ma, W., Berg, J., Yellen, G., 2007. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *J. Neurosci.* 27, 3618–3625.
- Maalouf, M., Rho, J.M., in press. Ketone bodies prevent impairment of long-term potentiation by hydrogen peroxide in hippocampal slices. *J. Neurosci. Res.*
- Maalouf, M., Sullivan, P.G., Davis, L., Kim, D.Y., Rho, J.M., 2007. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. *Neuroscience* 145, 256–264.
- Maggirwar, S.B., Sarmiere, P.D., Dewhurst, S., Freeman, R.S., 1998. Nerve growth factor-dependent activation of NF-kappaB contributes to survival of sympathetic neurons. *J. Neurosci.* 18, 10356–10365.
- Mantis, J.G., Centeno, N.A., Todorova, M.T., McGowan, R., Seyfried, T.N., 2004. Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: role of glucose and ketone bodies. *Nutr. Metab. (Lond)* 1, 11.
- Mariani, E., Polidori, M.C., Cherubini, A., Mecocci, P., 2005. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* 827, 65–75.
- Marie, C., Bralet, A.M., Gueldry, S., Bralet, J., 1990. Fasting prior to transient cerebral ischemia reduces delayed neuronal necrosis. *Metab. Brain. Dis.* 5, 65–75.
- Marini, A.M., Jiang, X., Wu, X., Tian, F., Zhu, D., Okagaki, P., Lipsky, R.H., 2004. Role of brain-derived neurotrophic factor and NF-kappaB in neuronal plasticity and survival: from genes to phenotype. *Restor. Neurol. Neurosci.* 22, 121–130.
- Markowska, A.L., 1999. Life-long diet restriction failed to retard cognitive aging in Fischer-344 rats. *Neurobiol. Aging* 20, 177–189.
- Markowska, A.L., Mooney, M., Sonntag, W.E., 1998. Insulin-like growth factor-1 ameliorates age-related behavioral deficits. *Neuroscience* 87, 559–569.

- Markowska, A.L., Savonenko, A., 2002. Retardation of cognitive aging by life-long diet restriction: implications for genetic variance. *Neurobiol. Aging* 23, 75–86.
- Marmorstein, R., 2004. Structure and chemistry of the Sir2 family of NAD⁺-dependent histone/protein deacetylases. *Biochem. Soc. Trans.* 32, 904–909.
- Marsh, E.B., Freeman, J.M., Kossoff, E.H., Vining, E.P., Rubenstein, J.E., Pyzik, P.L., Hemingway, C., 2006. The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. *Epilepsia* 47, 425–430.
- Marthaler, N., Rho, J.M., Simeone, T., Scheck, A., 2006. Ketone Bodies Inhibit Brain Tumor Cell Growth in vitro. Society for Neuroscience, Atlanta, GA.
- Martillotti, J., Weinshenker, D., Liles, L.C., Eagles, D.A., 2006. A ketogenic diet and knockout of the norepinephrine transporter both reduce seizure severity in mice. *Epilepsy Res.* 68, 207–211.
- Martin, B., Mattson, M.P., Maudsley, S., 2006. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res. Rev.* 5, 332–353.
- Martin, L.J., 2006. Mitochondriopathy in Parkinson disease and amyotrophic lateral sclerosis. *J. Neuropathol. Exp. Neurol.* 65, 1103–1110.
- Mascarucci, P., Taub, D., Sacconi, S., Paloma, M.A., Dawson, H., Roth, G.S., Lane, M.A., Ingram, D.K., 2002. Cytokine responses in young and old rhesus monkeys: effect of caloric restriction. *J. Interferon Cytokine Res.* 22, 565–571.
- Masino, S.A., Geiger, J.D., 2008. Are purines mediators of the anticonvulsant/neuroprotective effects of ketogenic diets? *Trends Neurosci.* 31, 273–278.
- Masoro, E.J., 1993. Dietary restriction and aging. *J. Am. Geriatr. Soc.* 41, 994–999.
- Masoro, E.J., Yu, B.P., Bertrand, H.A., 1982. Action of food restriction in delaying the aging process. *Proc. Natl. Acad. Sci. U. S. A.* 79, 4239–4241.
- Massieu, L., Del Río, P., Montiel, T., 2001. Neurotoxicity of glutamate uptake inhibition in vivo: correlation with succinate dehydrogenase activity and prevention by energy substrates. *Neuroscience* 106, 669–677.
- Massieu, L., Haces, M.L., Montiel, T., Hernández-Fonseca, K., 2003. Acetoacetate protects hippocampal neurons against glutamate-mediated neuronal damage during glycolysis inhibition. *Neuroscience* 120, 365–378.
- Masuda, R., Monahan, J.W., Kashiwaya, Y., 2005. D-beta-hydroxybutyrate is neuroprotective against hypoxia in serum-free hippocampal primary cultures. *J. Neurosci. Res.* 80, 501–509.
- Maswood, N., Young, J., Tilmont, E., Zhang, Z., Gash, D.M., Gerhardt, G.A., Grondin, R., Roth, G.S., Mattison, J., Lane, M.A., Carson, R.E., Cohen, R.M., Mouton, P.R., Quigley, C., Mattson, M.P., Ingram, D.K., 2004. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc. Natl. Acad. Sci. U. S. A.* 101, 18171–18176.
- Mattiasson, G., Shamloo, M., Gido, G., Mathi, K., Tomasevic, G., Yi, S., Warden, C.H., Castilho, R.F., Melcher, T., Gonzalez-Zulueta, M., Nikolich, K., Wieloch, T., 2003. Uncoupling protein-2 prevents neuronal death and diminishes brain dysfunction after stroke and brain trauma. *Nat. Med.* 9, 1062–1068.
- Mattson, M.P., 2003. Gene-diet interactions in brain aging and neurodegenerative disorders. *Ann. Intern. Med.* 139, 441–444.
- Mattson, M.P., 2005. Energy intake, meal frequency, and health: a neurobiological perspective. *Annu. Rev. Nutr.* 25, 237–260.
- Mattson, M.P., 2008a. Hormesis defined. *Ageing Res. Rev.* 7, 1–7.
- Mattson, M.P., 2008b. Dietary factors, hormesis and health. *Ageing Res. Rev.* 7, 43–48.
- Mattson, M.P., Camandola, S., 2001. NF-kappaB in neuronal plasticity and neurodegenerative disorders. *J. Clin. Invest.* 107, 247–254.
- Mattson, M.P., Cheng, A., 2006. Neurohormetic phytochemicals: low-dose toxins that induce adaptive neuronal stress responses. *Trends Neurosci.* 29, 632–639.
- Mattson, M.P., Duan, W., Guo, Z., 2003. Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms. *J. Neurochem.* 84, 417–431.
- Mattson, M.P., Goodman, Y., Luo, H., Fu, W., Furukawa, K., 1997. Activation of NF-kappaB protects hippocampal neurons against oxidative stress-induced apoptosis: evidence for induction of manganese superoxide dismutase and suppression of peroxynitrite production and protein tyrosine nitration. *J. Neurosci. Res.* 49, 681–697.
- Mattson, M.P., Magnus, T., 2006. Ageing and neuronal vulnerability. *Nat. Rev. Neurosci.* 7, 278–294.
- Mattson, M.P., Wan, R., 2005. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. *J. Nutr. Biochem.* 16, 129–137.
- Mavropoulos, J.C., Isaacs, W.B., Pizzo, S.V., Freedland, S.J., 2006. Is there a role for a low-carbohydrate ketogenic diet in the management of prostate cancer? *Urology* 68, 15–18.
- McCarter, R., Masoro, E.J., Yu, B.P., 1985. Does food restriction retard aging by reducing the metabolic rate? *Am. J. Physiol.* 248, E488–E490.
- Means, L.W., Higgins, J.L., Fernandez, T.J., 1993. Mid-life onset of dietary restriction extends life and prolongs cognitive functioning. *Physiol. Behav.* 54, 503–508.
- Merry, B.J., 2002. Molecular mechanisms linking calorie restriction and longevity. *Int. J. Biochem. Cell Biol.* 34, 1340–1354.
- Merry, B.J., 2004. Oxidative stress and mitochondrial function with aging—the effects of calorie restriction. *Ageing Cell* 3, 7–12.
- Middleton, G., Hamanoue, M., Enokido, Y., Wyatt, S., Pennica, D., Jaffray, E., Hay, R.T., Davies, A.M., 2000. Cytokine-induced nuclear factor kappa B activation promotes the survival of developing neurons. *J. Cell Biol.* 148, 325–332.
- Mockett, R.J., Cooper, T.M., Orr, W.C., Sohal, R.S., 2006. Effects of caloric restriction are species-specific. *Biogerontology* 7, 157–160.
- Molteni, R., Barnard, R.J., Ying, Z., Roberts, C.K., Gómez-Pinilla, F., 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 112, 803–814.
- Moore, S.A., Lopez, A., Richardson, A., Pahlavani, M.A., 1998. Effect of age and dietary restriction on expression of heat shock protein 70 in rat alveolar macrophages. *Mech. Ageing Dev.* 104, 59–73.
- Moreira, P.I., Honda, K., Zhu, X., Nunomura, A., Casadesus, G., Smith, M.A., Perry, G., 2006. Brain and brawn: parallels in oxidative strength. *Neurology* 66, S97–S101.
- Moro, M.A., Almeida, A., Bolaños, J.P., Lizasoain, I., 2005. Mitochondrial respiratory chain and free radical generation in stroke. *Free Radic. Biol. Med.* 39, 1291–1304.
- Morris, A.A., 2005. Cerebral ketone body metabolism. *J. Inherit. Metab. Dis.* 28, 109–121.
- Motta, M.C., Divecha, N., Lemieux, M., Kamel, C., Chen, D., Gu, W., Bultsma, Y., McBurney, M., Guarente, L., 2004. Mammalian SIRT1 represses forkhead transcription factors. *Cell* 116, 551–563.
- Muchowski, P.J., 2002. Protein misfolding, amyloid formation, and neurodegeneration: a critical role for molecular chaperones? *Neuron* 35, 9–12.
- Muller-Schwarze, A.B., Tandon, P., Liu, Z., Yang, Y., Holmes, G.L., Stafstrom, C.E., 1999. Ketogenic diet reduces spontaneous seizures and mossy fiber sprouting in the kainic acid model. *Neuroreport* 10, 1517–1522.
- Munoz-Fernandez, M.A., Fresno, M., 1998. The role of tumour necrosis factor, interleukin 6, interferon-gamma and inducible nitric oxide synthase in the development and pathology of the nervous system. *Prog. Neurobiol.* 56, 307–340.

- Natarajan, C., Muthian, G., Barak, Y., Evans, R.M., Bright, J.J., 2003. Peroxisome proliferator-activated receptor-gamma-deficient heterozygous mice develop an exacerbated neural antigen-induced Th1 response and experimental allergic encephalomyelitis. *J. Immunol.* 171, 5743–5750.
- Neal, E.G., Chaffe, H., Edwards, N., Lawson, M.S., Schwartz, R.H., Cross, J.H., 2008a. Growth of children on classical and medium-chain triglyceride ketogenic diets. *Pediatrics* 122, e334–e340.
- Neal, E.G., Chaffe, H., Schwartz, R.H., Lawson, M.S., Edwards, N., Fitzsimmons, G., Whitney, A., Cross, J.H., 2008b. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol.* 7, 500–506.
- Nehlig, A., 2004. Brain uptake and metabolism of ketone bodies in animal models. *Prostaglandins Leukot. Essent. Fatty Acids* 70, 265–275.
- Nicholls, D.G., 2004. Mitochondrial dysfunction and glutamate excitotoxicity studied in primary neuronal cultures. *Curr. Mol. Med.* 4, 149–177.
- Niino, M., Iwabuchi, K., Kikuchi, S., Ato, M., Morohashi, T., Ogata, A., Tashiro, K., Onoé, K., 2001. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma. *J. Neuroimmunol.* 116, 40–48.
- Nemoto, S., Fergusson, M.M., Finkel, T., 2005. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1 α . *J. Biol. Chem.* 280, 16456–16460.
- Nisoli, E., Tonello, C., Cardile, A., Cozzi, V., Bracale, R., Tedesco, L., Falcone, S., Valerio, A., Cantoni, O., Clementi, E., Mocada, S., Carruba, M.O., 2005. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science* 310, 314–317.
- Noh, H.S., Kim, Y.S., Lee, H.P., Chung, K.M., Kim, D.W., Kang, S.S., Cho, G.J., Choi, W.S., 2003. The protective effect of a ketogenic diet on kainic acid-induced hippocampal cell death in the male ICR mice. *Epilepsy Res.* 53, 119–128.
- Noh, H.S., Lee, H.P., Kim, D.W., Kang, S.S., Cho, G.J., Rho, J.M., Choi, W.S., 2004. A cDNA microarray analysis of gene expression profiles in rat hippocampus following a ketogenic diet. *Brain Res. Mol. Brain. Res.* 129, 80–87.
- Noh, H.S., Kang, S.S., Kim, D.W., Kim, Y.H., Park, C.H., Han, J.Y., Cho, G.J., Choi, W.S., 2005a. Ketogenic diet increases calbindin-D28k in the hippocampi of male ICR mice with kainic acid seizures. *Epilepsy Res.* 65, 153–159.
- Noh, H.S., Kim, D.W., Kang, S.S., Cho, G.J., Choi, W.S., 2005b. Ketogenic diet prevents clusterin accumulation induced by kainic acid in the hippocampus of male ICR mice. *Brain Res.* 1042, 114–118.
- Noh, H.S., Hah, Y.S., Nilufar, R., Han, J., Bong, J.H., Kang, S.S., Cho, G.J., Choi, W.S., 2006a. Acetoacetate protects neuronal cells from oxidative glutamate toxicity. *J. Neurosci. Res.* 83, 702–709.
- Noh, H.S., Kim, Y.S., Kim, Y.H., Han, J.Y., Park, C.H., Kang, A.K., Shin, H.S., Kang, S.S., Cho, G.J., Choi, W.S., 2006b. Ketogenic diet protects the hippocampus from kainic acid toxicity by inhibiting the dissociation of bad from 14-3-3. *J. Neurosci. Res.* 84, 1829–1836.
- Nordli Jr., D.R., Kuroda, M.M., Carroll, J., Koenigsberger, D.Y., Hirsch, L.J., Bruner, H.J., Seidel, W.T., De Vivo, D.C., 2001. Experience with the ketogenic diet in infants. *Pediatrics* 108, 129–133.
- Okada, M., Nakanishi, H., Amamoto, T., Urae, R., Ando, S., Yazawa, K., Fujiwara, M., 2003. How does prolonged caloric restriction ameliorate age-related impairment of long-term potentiation in the hippocampus? *Brain Res. Mol. Brain. Res.* 111, 175–181.
- Onyango, I.G., Khan, S.M., 2006. Oxidative stress, mitochondrial dysfunction, and stress signaling in Alzheimer's disease. *Curr. Alzheimer Res.* 3, 339–349.
- Park, S.K., Prolla, T.A., 2005. Lessons learned from gene expression profile studies of aging and caloric restriction. *Ageing Res. Rev.* 4, 55–65.
- Parker, J.A., Arango, M., Abderrahmane, S., Lambert, E., Tourette, C., Catoire, H., Néri, C., 2005. Resveratrol rescues mutant polyglutamine cytotoxicity in nematode and mammalian neurons. *Nat. Genet.* 37, 349–350.
- Patel, A.C., Nunez, N.P., Perkins, S.N., Barrett, J.C., Hursting, S.D., 2004. Effects of energy balance on cancer in genetically altered mice. *J. Nutr.* 134, 3394S–3398S.
- Pedersen, W.A., Culmsee, C., Ziegler, D., Herman, J.P., Mattson, M.P., 1999. Aberrant stress response associated with severe hypoglycemia in a transgenic mouse model of Alzheimer's disease. *J. Mol. Neurosci.* 13, 159–165.
- Pedersen, W.A., Mattson, M.P., 1999. No benefit of dietary restriction on disease onset or progression in amyotrophic lateral sclerosis Cu/Zn-superoxide dismutase mutant mice. *Brain Res.* 833, 117–120.
- Pereira, M.P., Hurtado, O., Cárdenas, A., Alonso-Escolano, D., Boscá, L., Vivancos, J., Nombela, F., Leza, J.C., Lorenzo, P., Lizasoain, I., Moro, M.A., 2005. The nonthiazolidinedione PPAR γ agonist L-796,449 is neuroprotective in experimental stroke. *J. Neuropathol. Exp. Neurol.* 64, 797–805.
- Pereira, M.P., Hurtado, O., Cárdenas, A., Boscá, L., Castilla, J., Dávalos, A., Vivancos, J., Serena, J., Lorenzo, P., Lizasoain, I., Moro, M.A., 2006. Rosiglitazone and 15-deoxy-Delta12, 14-prostaglandin J2 cause potent neuroprotection after experimental stroke through noncompletely overlapping mechanisms. *J. Cereb. Blood Flow Metab.* 26, 218–229.
- Perkins, N.D., 2007. Integrating cell-signalling pathways with NF- κ B and IKK function. *Nat. Rev. Mol. Cell Biol.* 8, 49–62.
- Picard, F., Kurtev, M., Chung, N., Topark-Ngarm, A., Senawong, T., Machado De Oliveira, R., Leid, M., McBurney, M.W., Guarente, L., 2004. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR- γ . *Nature* 429, 771–776.
- Pitsikas, N., Algeri, S., 1992. Deterioration of spatial and nonspatial reference and working memory in aged rats: protective effect of life-long calorie restriction. *Neurobiol. Aging* 13, 369–373.
- Pitsikas, N., Carli, M., Fidecka, S., Algeri, S., 1990. Effect of life-long hypocaloric diet on age-related changes in motor and cognitive behavior in a rat population. *Neurobiol. Aging* 11, 417–423.
- Plunet, W.T., Streijger, F., Lam, C.K., Lee, J.H., Liu, J., Tetzlaff, W., in press. Dietary restriction started after spinal cord injury improves functional recovery. *Exp. Neurol.*
- Poynter, M.E., Daynes, R.A., 1998. Peroxisome proliferator-activated receptor alpha activation modulates cellular redox status, represses nuclear factor- κ B signaling, and reduces inflammatory cytokine production in aging. *J. Biol. Chem.* 273, 32833–32841.
- Prins, M.L., Fujima, L.S., Hovda, D.A., 2005. Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury. *J. Neurosci. Res.* 82, 413–420.
- Pulsifer, M.B., Gordon, J.M., Brandt, J., Vining, E.P., Freeman, J.M., 2001. Effects of ketogenic diet on development and behavior: preliminary report of a prospective study. *Dev. Med. Child Neurol.* 43, 301–306.
- Qin, W., Chachich, M., Lane, M., Roth, G., Bryant, M., de Cabo, R., Ottinger, M.A., Mattison, J., Ingram, D., Gandy, S., Pasinetti, G.M., 2006a. Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (*Saimiri sciureus*). *J. Alzheimers Dis.* 10, 417–422.
- Qin, W., Yang, T., Ho, L., Zhao, Z., Wang, J., Chen, L., Zhao, W., Thyagarajan, M., MacGrogan, D., Rodgers, J.T., Puigserver, P., Sadoshima, J., Deng, H., Pedrini, S., Gandy, S., Sauve, A.A., Pasinetti, G.M., 2006b. Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. *J. Biol. Chem.* 281, 21745–21754.

- Rajdev, S., Hara, K., Kokubo, Y., Mestrl, R., Dillmann, W., Weinstein, P.R., Sharp, F.R., 2000. Mice overexpressing rat heat shock protein 70 are protected against cerebral infarction. *Ann. Neurol.* 47, 782–791.
- Rankin, J.W., Shute, M., Heffron, S.P., Saker, K.E., 2006. Energy restriction but not protein source affects antioxidant capacity in athletes. *Free Radic. Biol. Med.* 41, 1001–1009.
- Rasmussen, M.H., Juul, A., Kjems, L.L., Hilsted, J., 2006. Effects of short-term caloric restriction on circulating free IGF-I, acid-labile subunit, IGF-binding proteins (IGFBPs)-1–4, and IGFBPs-1–3 protease activity in obese subjects. *Eur. J. Endocrinol.* 155, 575–581.
- Reddy, P.H., 2006. Mitochondrial oxidative damage in aging and Alzheimer's disease: implications for mitochondrially targeted antioxidant therapeutics. *J. Biomed. Biotechnol.* 2006, 31372.
- Redman, L.M., Martin, C.K., Williamson, D.A., Ravussin, E., 2008. Effect of caloric restriction in non-obese humans on physiological, psychological and behavioral outcomes. *Physiol. Behav.* 94, 643–648.
- Reger, M.A., Henderson, S.T., Hale, C., Cholerton, B., Baker, L.D., Watson, G.S., Hyde, K., Chapman, D., Crafts, S., 2004. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol. Aging* 25, 311–314.
- Rho, J.M., Anderson, G.D., Donevan, S.D., White, H.S., 2002. Acetoacetate, acetone, and dibenzylamine (a contaminant in L-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions in vivo. *Epilepsia* 43, 358–361.
- Richter, C., Ghafourifar, P., 1999. Ceramide induces cytochrome c release from isolated mitochondria. *Biochem. Soc. Symp.* 66, 27–31.
- Rimvall, K., Martin, D.L., 1992. Increased intracellular gamma-aminobutyric acid selectively lowers the level of the larger of two glutamate decarboxylase proteins in cultured GABAergic neurons from rat cerebral cortex. *J. Neurochem.* 58, 158–166.
- Rimvall, K., Martin, D.L., 1994. The level of GAD67 protein is highly sensitive to small increases in intraneuronal gamma-aminobutyric acid levels. *J. Neurochem.* 62, 1375–1381.
- Rimvall, K., Sheikh, S.N., Martin, D.L., 1993. Effects of increased gamma-aminobutyric acid levels on GAD67 protein and mRNA levels in rat cerebral cortex. *J. Neurochem.* 60, 714–720.
- Rincon, M., Rudin, E., Barzilai, N., 2005. The insulin/IGF-1 signaling in mammals and its relevance to human longevity. *Exp. Gerontol.* 40, 873–877.
- Risner, M.E., Saunders, A.M., Altman, J.F., Ormandy, G.C., Craft, S., Foley, I.M., Zvartau-Hind, M.E., Hosford, D.A., Roses, A.D., Rosiglitazone in Alzheimer's Disease Study Group, 2006. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J.* 6, 246–254.
- Rodgers, J.T., Lerin, C., Gerhart-Hines, Z., Puigserver, P., 2008. Metabolic adaptations through the PGC-1 alpha and SIRT1 pathways. *FEBS Lett.* 582, 46–53.
- Rogina, B., Helfand, S.L., 2004. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. *Proc. Natl. Acad. Sci. U. S. A.* 101, 15998–16003.
- Russo, V.C., Gluckman, P.D., Feldman, E.L., Werther, G.A., 2005. The insulin-like growth factor system and its pleiotropic functions in brain. *Endocr. Rev.* 26, 916–943.
- Ruvolo, P.P., Clark, W., Mumby, M., Gao, F., May, W.S., 2002. A functional role for the B56 alpha-subunit of protein phosphatase 2A in ceramide-mediated regulation of Bcl2 phosphorylation status and function. *J. Biol. Chem.* 277, 22847–22852.
- Ruvolo, P.P., Deng, X., Ito, T., Carr, B.K., May, W.S., 1999. Ceramide induces Bcl2 dephosphorylation via a mechanism involving mitochondrial PP2A. *J. Biol. Chem.* 274, 20296–20300.
- Santos-Pinto, F.N., Luz, J., Griggio, M.A., 2001. Energy expenditure of rats subjected to long-term food restriction. *Int. J. Food Sci. Nutr.* 52, 193–200.
- Santra, S., Gilkerson, R.W., Davidson, M., Schon, E.A., 2004. Ketogenic treatment reduces deleted mitochondrial DNAs in cultured human cells. *Ann. Neurol.* 56, 662–669.
- Sanz, A., Caro, P., Ibañez, J., Gómez, J., Gredilla, R., Barja, G., 2005. Dietary restriction at old age lowers mitochondrial oxygen radical production and leak at complex I and oxidative DNA damage in rat brain. *J. Bioenerg. Biomembr.* 37, 83–90.
- Sarkar, D., Fisher, P.B., 2006. Molecular mechanisms of aging-associated inflammation. *Cancer Lett.* 236, 13–23.
- Sastre, M., Dewachter, I., Landreth, G.E., Willson, T.M., Klockgether, T., van Leuven, F., Heneka, M.T., 2003. Nonsteroidal anti-inflammatory drugs and peroxisome proliferator-activated receptor-gamma agonists modulate immunostimulated processing of amyloid precursor protein through regulation of beta-secretase. *J. Neurosci.* 23, 9796–9804.
- Sastre, M., Dewachter, I., Rossner, S., Bogdanovic, N., Rosen, E., Borghgraef, P., Evert, B.O., Dumitrescu-Ozimek, L., Thal, D.R., Landreth, G., Walter, J., Klockgether, T., van Leuven, F., Heneka, M.T., 2006. Nonsteroidal anti-inflammatory drugs repress beta-secretase gene promoter activity by the activation of PPARgamma. *Proc. Natl. Acad. Sci. U. S. A.* 103, 443–448.
- Sauve, A.A., Wolberger, C., Schramm, V.L., Boeke, J.D., 2006. The biochemistry of sirtuins. *Annu. Rev. Biochem.* 75, 435–465.
- Savaskan, E., Olivieri, G., Meier, F., Seifritz, E., Wirz-Justice, A., Müller-Spahn, F., 2003. Red wine ingredient resveratrol protects from beta-amyloid neurotoxicity. *Gerontology* 49, 380–383.
- Schutz, B., Reimann, J., Dumitrescu-Ozimek, L., Kappes-Horn, K., Landreth, G.E., Schurmann, B., Zimmer, A., Heneka, M.T., 2005. The oral antidiabetic pioglitazone protects from neurodegeneration and amyotrophic lateral sclerosis-like symptoms in superoxide dismutase-G93A transgenic mice. *J. Neurosci.* 25, 7805–7812.
- Selsby, J.T., Judge, A.R., Yimlamai, T., Leeuwenburgh, C., Dodd, S.L., 2005. Life long calorie restriction increases heat shock proteins and proteasome activity in soleus muscles of Fisher 344 rats. *Exp. Gerontol.* 40, 37–42.
- Seyfried, T.N., Sanderson, T.M., El-Abbadi, M.M., McGowan, R., Mukherjee, P., 2003. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. *Br. J. Cancer.* 89, 1375–1382.
- Seyfried, T.N., Mukherjee, P., 2005. Targeting energy metabolism in brain cancer: review and hypothesis. *Nutr. Metab.* 2, 30.
- Seymour, K.J., Bluml, S., Sutherland, J., Sutherland, W., Ross, B.D., 1999. Identification of cerebral acetone by 1H-MRS in patients with epilepsy controlled by ketogenic diet. *Magma* 8, 33–42.
- Sharma, S., Kaur, G., 2005. Neuroprotective potential of dietary restriction against kainate-induced excitotoxicity in adult male Wistar rats. *Brain Res. Bull.* 67, 482–491.
- Shimazu, T., Inoue, I., Araki, N., Asano, Y., Sawada, M., Furuya, D., Nagoya, H., Greenberg, J.H., 2005. A peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not in permanent ischemia. *Stroke* 36, 353–359.
- Shimura, H., Schwartz, D., Gugi, S.P., Kosik, K.S., 2004. CHIP-Hsc70 complex ubiquitinates phosphorylated tau and enhances cell survival. *J. Biol. Chem.* 279, 4869–4876.
- Silva, M.C., Rocha, J., Pires, C.S., Ribeiro, L.C., Brolese, G., Leite, M.C., Almeida, L.M., Tramontina, F., Ziegler, D.R., Gonçalves, C.A., 2005. Transitory gliosis in the CA3 hippocampal region in rats fed on a ketogenic diet. *Nutr. Neurosci.* 8, 259–264.
- Sirven, J., Whedon, B., Caplan, D., Liporace, J., Glosser, D., O'Dwyer, J., Sperling, M.R., 1999. The ketogenic diet for intractable epilepsy in adults: preliminary results. *Epilepsia* 40, 1721–1726.
- Smith, W.J., Underwood, L.E., Clemmons, D.R., 1995. Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults. *J. Clin. Endocrinol. Metab.* 80, 443–449.
- Sohal, R.S., Agarwal, S., Candas, M., Forster, M.J., Lal, H., 1994. Effect of age and caloric restriction on DNA oxidative damage

- in different tissues of C57BL/6 mice. *Mech. Ageing Dev.* 76, 215–224.
- Sonntag, W.E., Ramsey, M., Carter, C.S., 2005. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. *Ageing Res. Rev.* 4, 195–212.
- Spaulding, C.C., Walford, R.L., Effros, R.B., 1997. Calorie restriction inhibits the age-related dysregulation of the cytokines TNF-alpha and IL-6 in C3B10RF1 mice. *Mech. Ageing Dev.* 93, 87–94.
- Squires, J.E., Sun, J., Caffrey, J.L., Yoshishige, D., Mallet, R.T., 2003. Acetoacetate augments beta-adrenergic inotropism of stunned myocardium by an antioxidant mechanism. *Am. J. Physiol. Heart Circ. Physiol.* 284, H1340–H1347.
- Sreekumar, R., Unnikrishnan, J., Fu, A., Nygren, J., Short, K.R., Shimke, J., Barazzoni, R., Nair, K.S., 2002. Effects of caloric restriction on mitochondrial function and gene transcripts in rat muscle. *Am. J. Physiol. Endocrinol. Metab.* 283, E38–E43.
- Stafstrom, C.E., Wang, C., Jensen, F.E., 1999. Electrophysiological observations in hippocampal slices from rats treated with the ketogenic diet. *Dev. Neurosci.* 21, 393–399.
- Strokin, M., Chechneva, O., Reymann, K.G., Reiser, G., 2006. Neuroprotection of rat hippocampal slices exposed to oxygen-glucose deprivation by enrichment with docosahexaenoic acid and by inhibition of hydrolysis of docosahexaenoic acid-containing phospholipids by calcium independent phospholipase A2. *Neuroscience* 140, 547–553.
- Sullivan, P.G., Dubé, C., Dorenbos, K., Steward, O., Baram, T.Z., 2003. Mitochondrial uncoupling protein-2 protects the immature brain from excitotoxic neuronal death. *Ann. Neurol.* 53, 711–717.
- Sullivan, P.G., Rabchevsky, A.G., Keller, J.N., Lovell, M., Sodhi, A., Hart, R.P., Scheff, S.W., 2004a. Intrinsic differences in brain and spinal cord mitochondria: implication for therapeutic interventions. *J. Comp. Neurol.* 474, 524–534.
- Sullivan, P.G., Rippey, N.A., Dorenbos, K., Concepcion, R.C., Agarwal, A.K., Rho, J.M., 2004b. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann. Neurol.* 55, 576–580.
- Sultan, I., Senkal, C.E., Ponnusamy, S., Bielawski, J., Szulc, Z., Bielawaska, A., Hannun, Y.A., Ogretmen, B., 2006. Regulation of the sphingosine-recycling pathway for ceramide generation by oxidative stress, and its role in controlling c-Myc/Max function. *Biochem. J.* 393, 513–521.
- Sundararajan, S., Gamboa, J.L., Victor, N.A., Wanderi, E.W., Lust, W.D., Landreth, G.E., 2005. Peroxisome proliferator-activated receptor-gamma ligands reduce inflammation and infarction size in transient focal ischemia. *Neuroscience* 130, 685–696.
- Sundararajan, S., Jiang, Q., Heneka, M., Landreth, G., 2006. PPARgamma as a therapeutic target in central nervous system diseases. *Neurochem. Int.* 49, 136–144.
- Suzuki, M., Suzuki, M., Kitamura, Y., Mori, S., Sato, K., Dohi, S., Sato, T., Matsuura, A., Hiraide, A., 2002. Beta-hydroxybutyrate, a cerebral function improving agent, protects rat brain against ischemic damage caused by permanent and transient focal cerebral ischemia. *Jpn. J. Pharmacol.* 89, 36–43.
- Suzuki, M., Suzuki, M., Sato, K., Dohi, S., Sato, T., Matsuura, A., Hiraide, A., 2001. Effect of beta-hydroxybutyrate, a cerebral function improving agent, on cerebral hypoxia, anoxia and ischemia in mice and rats. *Jpn. J. Pharmacol.* 87, 143–150.
- Szot, P., Weinshenker, D., Rho, J.M., Storey, T.W., Schwartzkroin, P.A., 2001. Norepinephrine is required for the anticonvulsant effect of the ketogenic diet. *Brain Res. Dev. Brain Res.* 129, 211–214.
- Taha, A.Y., Ryan, M.A., Cunnane, S.C., 2005. Despite transient ketosis, the classic high-fat ketogenic diet induces marked changes in fatty acid metabolism in rats. *Metabolism* 54, 1127–1132.
- Tai, K.K., Truong, D.D., 2007. Ketogenic diet prevents seizure and reduces myoclonic jerks in rats with cardiac arrest-induced cerebral hypoxia. *Neurosci. Lett.* 425, 34–38.
- Tai, K.K., Nguyen, N., Pham, L., Truong, D.D., 2008. Ketogenic diet prevents cardiac arrest-induced cerebral ischemic neurodegeneration. *J. Neural. Transm.* 115, 1011–1017.
- Tang, B.L., 2006. SIRT1, neuronal cell survival and the insulin/IGF-1 aging paradox. *Neurobiol. Aging* 27, 501–505.
- Thavendiranathan, P., Mendonca, A., Dell, C., Likhodii, S.S., Musa, K., Iracleous, C., Cunnane, S.C., Burnham, W.M., 2000. The MCT ketogenic diet: effects on animal seizure models. *Exp. Neurol.* 161, 696–703.
- Thio, L.L., Wong, M., Yamada, K.A., 2000. Ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. *Neurology* 54, 325–331.
- Thrasivoulou, C., Soubeyre, V., Ridha, A., Giuliani, D., Giaroni, C., Michael, G.J., Saffrey, M.J., Cowen, T., 2006. Reactive oxygen species, dietary restriction and neurotrophic factors in age-related loss of myenteric neurons. *Ageing Cell* 5, 247–257.
- Tieu, K., Perier, C., Caspersen, C., Teismann, P., Wu, D.C., Yan, S.D., Naini, A., Vila, M., Jackson-Lewis, V., Ramasamy, R., Przedborski, S., 2003. D-beta-hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. *J. Clin. Invest.* 112, 892–901.
- Tissenbaum, H.A., Guarente, L., 2001. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. *Nature* 410, 227–230.
- Todorova, M.T., Tandon, P., Madore, R.A., Stafstrom, C.E., Seyfried, T.N., 2000. The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy. *Epilepsia* 41, 933–940.
- Tsuchiya, M., Dang, N., Kerr, E.O., Hu, D., Steffen, K.K., Oakes, J.A., Kennedy, B.K., Kaeberlein, M., 2006. Sirtuin-independent effects of nicotinamide on lifespan extension from calorie restriction in yeast. *Ageing Cell* 5, 505–514.
- Turens, J.F., 2003. Mitochondrial formation of reactive oxygen species. *J. Physiol.* 552, 335–344.
- Ugochukwu, N.H., Figgers, C.L., 2007. Caloric restriction inhibits up-regulation of inflammatory cytokines and TNF-alpha, and activates IL-10 and haptoglobin in the plasma of streptozotocin-induced diabetic rats. *J. Nutr. Biochem.* 18, 120–126.
- Valerio, A., Boroni, F., Benarese, M., Sarnico, I., Ghisi, V., Bresciani, L.G., Ferrario, M., Borsani, G., Spano, P., Pizzi, M., 2006. NF-kappaB pathway: a target for preventing beta-amyloid (Abeta)-induced neuronal damage and Abeta42 production. *Eur. J. Neurosci.* 23, 1711–1720.
- Valle, A., Guevara, R., García-Palmer, F.J., Roca, P., Oliver, J., 2008. Caloric restriction retards the age-related decline in mitochondrial function of brown adipose tissue. *Rejuvenation Res.* 11, 597–604.
- Van der Auwera, I., Wera, S., Van Leuven, F., Henderson, S.T., 2005. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr. Metab. (Lond)* 2, 28.
- Vanitallie, T.B., Nonas, C., Di Rocco, A., Boyar, K., Hyams, K., Heysfield, S.B., 2005. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology* 64, 728–730.
- Vaziri, H., Dessain, S.K., Ng Eaton, E., Imai, S.I., Frye, R.A., Pandita, T.K., Guarente, L., Weinberg, R.A., 2001. hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. *Cell* 107, 149–159.
- Veech, R.L., 2004. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins Leukot. Essent. Fatty Acids* 70, 309–319.
- Veech, R.L., Chance, B., Kashiwaya, Y., Lardy, H.A., Cahill Jr., G.F., 2001. Ketone bodies, potential therapeutic uses. *IUBMB Life* 51, 241–247.
- Vining, E.P., Freeman, J.M., Ballaban-Gil, K., Camfield, C.S., Camfield, P.R., Holmes, G.L., Shinnar, S., Shuman, R., Trevathan, E., Wheless, J.W., 1998. A multicenter study of the efficacy of the ketogenic diet. *Arch. Neurol.* 55, 1433–1437.

- Virshup, D.M., 2000. Protein phosphatase 2A: a panoply of enzymes. *Curr. Opin. Cell Biol.* 12, 180–185.
- Wada, K., Nakajima, A., Katayama, K., Kudo, C., Shibuya, A., Kubota, N., Terauchi, Y., Tachibana, M., Miyoshi, H., Kamisaki, Y., Mayumi, T., Kadowaki, T., Blumberg, R.S., 2006. Peroxisome proliferator-activated receptor gamma-mediated regulation of neural stem cell proliferation and differentiation. *J. Biol. Chem.* 281, 12673–12681.
- Warrick, J.M., Chan, H.Y., Gray-Board, G.L., Chai, Y., Paulson, H.L., Bonini, N.M., 1999. Suppression of polyglutamine-mediated neurodegeneration in *Drosophila* by the molecular chaperone HSP70. *Nat. Genet.* 23, 425–428.
- Watson, G.S., Cholerton, B.A., Reger, M.A., Baker, L.D., Plymate, S.R., Asthana, S., Fishel, M.A., Kulstad, J.J., Green, P.S., Cook, D.G., Kahn, S.E., Keeling, M.L., Craft, S., 2005. Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am. J. Geriatr. Psychiatry* 13, 950–958.
- Widera, D., Mikenberg, I., Kaltschmidt, B., Kaltschmidt, C., 2006. Potential role of NF-kappaB in adult neural stem cells: the underrated steersman? *Int. J. Dev. Neurosci.* 24, 91–102.
- Willott, J.F., Erway, L.C., Archer, J.R., Harrison, D.E., 1995. Genetics of age-related hearing loss in mice. II. Strain differences and effects of caloric restriction on cochlear pathology and evoked response thresholds. *Hear Res.* 88, 143–155.
- Wing, R.R., Marcus, M.D., Blair, E.H., Burton, L.R., 1991. Psychological responses of obese type II diabetic subjects to very-low-calorie diet. *Diabetes Care* 14, 596–599.
- Wolf, G., 2006. Calorie restriction increases life span: a molecular mechanism. *Nutr. Rev.* 64, 89–92.
- Won, J.S., Singh, I., 2006. Sphingolipid signaling and redox regulation. *Free Radic. Biol. Med.* 40, 1875–1888.
- Xiao, Y., Li, X., 1999. Polyunsaturated fatty acids modify mouse hippocampal neuronal excitability during excitotoxic or convulsant stimulation. *Brain Res.* 846, 112–121.
- Xu, B., Michalski, B., Racine, R.J., Fahnstock, M., 2004. The effects of brain-derived neurotrophic factor (BDNF) administration on kindling induction, Trk expression and seizure-related morphological changes. *Neuroscience* 126, 521–531.
- Xu, X.P., Erichsen, D., Borjesson, S.I., Dahlin, M., Amark, P., Elinder, F., 2008. Polyunsaturated fatty acids and cerebrospinal fluid from children on the ketogenic diet open a voltage-gated K channel: a putative mechanism of antiseizure action. *Epilepsy Res.* (Epub ahead of print).
- Xu, X.P., Sun, R.P., Jin, R.F., 2006. Effect of ketogenic diet on hippocampus mossy fiber sprouting and GluR5 expression in kainic acid induced rat model. *Chin. Med. J. (Engl)* 119, 1925–1929.
- Yamada, K.A., Rensing, N., Thio, L.L., 2005. Ketogenic diet reduces hypoglycemia-induced neuronal death in young rats. *Neurosci. Lett.* 385, 210–214.
- Yanai, S., Okaichi, Y., Okaichi, H., 2004. Long-term dietary restriction causes negative effects on cognitive functions in rats. *Neurobiol. Aging* 25, 325–332.
- Yenari, M.A., Liu, J., Zheng, Z., Vexler, Z.S., Lee, J.E., Giffard, R.G., 2005. Antiapoptotic and anti-inflammatory mechanisms of heat-shock protein protection. *Ann. N. Y. Acad. Sci.* 1053, 74–83.
- Yeung, F., Hoberg, J.E., Ramsey, C.S., Keller, M.D., Jones, D.R., Frye, R.A., Mayo, M.W., 2004. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *Embo J.* 23, 2369–2380.
- Young, C., Gean, P.W., Chiou, L.C., Shen, Y.Z., 2000. Docosahexaenoic acid inhibits synaptic transmission and epileptiform activity in the rat hippocampus. *Synapse* 37, 90–94.
- Young, J.C., Agashe, V.R., Siegers, K., Hartl, F.J., 2004. Pathways of chaperone-mediated protein folding in the cytosol. *Nat. Rev. Mol. Cell Biol.* 5, 781–791.
- Yu, Z., Luo, H., Fu, W., Mattson, M.P., 1999. The endoplasmic reticulum stress-responsive protein GRP78 protects neurons against excitotoxicity and apoptosis: suppression of oxidative stress and stabilization of calcium homeostasis. *Exp. Neurol.* 155, 302–314.
- Yu, Z.F., Mattson, M.P., 1999. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. *J. Neurosci. Res.* 57, 830–839.
- Yudkoff, M., Daikhin, Y., Nissim, I., Horyn, O., Lazarow, A., Luhovyy, B., Wehrli, S., Nissim, I., 2005. Response of brain amino acid metabolism to ketosis. *Neurochem. Int.* 47, 119–128.
- Zabrocki, P., Van Hoof, C., Goris, J., Thevelein, J.M., Winderickx, J., Wera, S., 2002. Protein phosphatase 2A on track for nutrient-induced signalling in yeast. *Mol. Microbiol.* 43, 835–842.
- Zangarelli, A., Chanseume, E., Morio, B., Brugère, C., Mosoni, L., Rousset, P., Giraudet, C., Patrac, V., Gachon, P., Boirie, Y., Walrand, S., 2006. Synergistic effects of caloric restriction with maintained protein intake on skeletal muscle performance in 21-month-old rats: a mitochondria-mediated pathway. *Faseb J.* 20, 2439–2450.
- Zhao, Q., Stafstrom, C.E., Fu, D.D., Hu, Y., Holmes, G.L., 2004. Detrimental effects of the ketogenic diet on cognitive function in rats. *Pediatr. Res.* 55, 498–506.
- Zhao, X., Ou, Z., Grotta, J.C., Waxham, N., Aronowski, J., 2006a. Peroxisome-proliferator-activated receptor-gamma (PPARgamma) activation protects neurons from NMDA excitotoxicity. *Brain Res.* 1073–1074, 460–469.
- Zhao, Z., Lange, D.J., Voustantiouk, A., MacGrogan, D., Ho, L., Suh, J., Humala, N., Thiyagarajan, M., Wang, J., Pasinetti, G.M., 2006b. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. *BMC Neurosci.* 7, 29.
- Zhou, W., Mukherjee, P., Kiebish, M.A., Markis, W.T., Mantis, J.G., Seyfried, T.N., 2007. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. *Nutr. Metab. (Lond)* 4, 5.
- Ziegler, D.R., Ribeiro, L.C., Hagenn, M., Siqueira, I.R., Araújo, E., Torres, I.L., Gottfried, C., Netto, C.A., Gonçalves, C.A., 2003. Ketogenic diet increases glutathione peroxidase activity in rat hippocampus. *Neurochem. Res.* 28, 1793–1797.