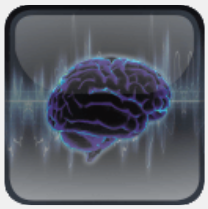

Ketogenic Diet and Metabolic Therapies: Expanded Roles in Health and Disease

Edited by Susan A Masino, PHD

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Alzheimer’s Disease: Causes and Treatment

Chapter: Alzheimer’s Disease: Causes and Treatment
Author(s): Richard L. Veech, and M. Todd King
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Incidence

The prevalence of Alzheimer’s disease is strongly correlated with age. In a general community, 3% of those between 65 and 74 years of age had probable Alzheimer’s disease, compared with 18.7% of those between 75 and 84 years. In those over 85 the prevalence rose to 47.2% (Evans et al., 1989). In the United States it was estimated that in 2013 there were 5.2 million patients with Alzheimer’s disease, costing $203 billion in direct medical care and another $216 billion in care from unpaid caregivers (Thies & Bleiler 2013).

Predisposing Factors

The major predisposing factor for Alzheimer’s disease is age. Women are more likely to be affected than men. Diabetes, obesity and

lack of exercise predispose to the disease. The genetic environmental, nutritional and metabolic risk factors are discussed below.

Genetic

Only about 10% of the cases of Alzheimer’s disease are familial; about 90% are classed as “sporadic,” with age being the major risk factor. A primary cause of the aging-associated damage is free radical damage (Harman, 1956). Factors other than aging can predispose individuals to the onset of Alzheimer’s disease, the major genetic factor being the apolipoprotein E genotype (Strittmatter and Roses, 1995). Apolipoprotein E (ApoE) is the lipoprotein involved in transport of lipids and cholesterol in the circulatory system. There are three major alleles, ApoE-2, ApoE-3, and ApoE-4. In one large kindred group of the ApoE-4 genotype, the onset of clinical symptoms was between 55 and 78 years of age (Martin et al., 1997), demonstrating that this genetic factor predisposes individuals to a “late-onset” form of the disease.

Early-onset Alzheimer’s disease is associated with three genes that increase the production or deposition of β-amyloid protein. These include the precursor of amyloid protein, found in Alzheimer’s disease and in Down syndrome. Missense mutations in the presenilin 1 and 2 genes, which code for several secretases, involved in the catabolism of amyloid, lead to the early onset of an aggressive familial form of Alzheimer’s disease. Mutations in these genes result in the onset of Alzheimer’s disease, often in the 40s or 50s, but occasionally in the 30s. The increased incidence of early Alzheimer’s disease with genetic abnormalities in amyloid suggests that amyloid can exacerbate the inhibition of pyruvate dehydrogenase (PDH) (Hoshi et al., 1996). It follows that inhibition of cerebral PDH could be the primary cause of Alzheimer’s disease and the primary factor to be overcome in its treatment and prevention (Kashiwaya et al., 2000).

Environmental

Radiation is known to induce production of free radicals, or reactive oxygen species (ROS), and induce oxidant damage (Alexander and Stacey, 1959; Riley, 1994; Szilard, 1959). Low levels of radiation, under 5 Gy, can induce both cognitive dysfunction and the pathological changes of neurodegeneration seen in both Parkinson’s and Alzheimer’s disease (Kempf et al., 2013). In cultured neurons, radiation also induced tau phosphorylation (Li et al., 2014), characteristic of both Alzheimer’s disease and frontotemporal dementia. These effects have application to cancer therapy, prolonged space flight, and exposure to nuclear radiation (Li et al., 2014).

Traumatic brain injury (TBI) prematurely causes pathology similar to both Alzheimer’s and Parkinson’s disease (Dekosky et al., 2013; DeKosky et al., 2010). In addition to the accumulation of amyloid and phosphorylated tau, patients with TBI can develop both cognitive impairment and Parkinsonian symptoms. In contrast to the damaging effects of brain trauma, physical exercise can retard neurodegeneration and decrease inflammation in brain (Cotman et al., 2007).

Nutritional and Metabolic

Type II diabetes is strongly associated with both vascular dementia and Alzheimer’s dementia (Ott et al., 1996; Xu et al., 2009). Diabetes has been shown to accompany an increase in dementia in twin studies (Kuusisto et al., 1997). Conversely, caloric restriction or intermittent fasting ameliorates amyloid accumulation (Mouton et al., 2009) and the cognitive deficits in the triple transgenic mouse models of Alzheimer’s disease (Halagappa et al., 2007).

Pathophysiology

The original clinical and pathological description of neurofibrillary tangles, amyloid plaques, paranoid ideation, and memory loss was given by Alois Alzheimer in 1907 (Alzheimer, 1907). Transgenic mouse models based on mutations in amyloid precursor protein and its processing show accumulation of amyloid and phosphorylated tau protein in their brains (Johnson-Wood et al., 1997). The most prevalent hypothesis to explain the pathophysiology of Alzheimer’s disease derives from the pathological findings described by Alzheimer of increased amyloid plaques and phosphorylated tau tangles. The theory that Alzheimer’s disease results from amyloid accumulation in the brain has been called the amyloid hypothesis (Selkoe, 1997). Alternatively, it is possible that an inhibition of brain PDH due to insulin resistance in the brain results in a deficiency in substrate availability in the tricarboxylic acid (TCA) cycle. Thus brain energy deficit and mild cognitive impairment can precede amyloid accumulation (Biessels and Reagan, 2015; Hoyer, 1991, 1996; Kuusisto et al., 1997; Talbot et al., 2012; Willette et al., 2015). The accumulation of amyloid and phosphorylated tau protein exacerbates the preexisting inhibition of PDH (Hoshi et al., 1997a; Hoshi et al., 1996). Mutations in amyloid precursor protein (APP) are found in comparatively rare early-onset forms of the disease. Amyloid accumulates in brains of subjects with Alzheimer’s disease, but its accumulation does not correlate, either quantitatively or temporally, with the cognitive impairment or loss of brain volume (Josephs et al., 2008).

Alterations in the alleles of the ApoE-4 lipoprotein (Roses, 2006) involved in cholesterol and lipid transport, are associated with predisposition to the more common late-onset form of the disease. While the association of the ApoE-4 allele with late-onset Alzheimer’s has been confirmed by exhaustive genomewide association studies (GWAS), no other major genetic links to Alzheimer’s disease were found (Naj et al., 2014). The majority of cases of late-onset Alzheimer’s disease are not associated with any identified genetic factor but are simply correlated with increased age. Alzheimer’s disease is, however, strongly correlated with insulin resistance both epidemiologically and pathophysiologically (Kuusisto et al., 1997; Ott et al., 1996; Reaven et al., 1990; Xu et al., 2009). The incidence of the disease can be increased by free radical damage, radiation, TBI, immune dysfunction, and indolence (Selkoe, 2001), all of which are also associated with insulin resistance (Zhai et al., 2011).

Evidence suggests that amyloid β-1-42 fragments? can stimulate the phosphorylation and hence the inhibition of PDH. This amyloid fragment can exert toxic effects on hippocampal neurons in culture (Kashiwaya et al., 2000), which is compatible with the report that amyloid can inhibit PDH (Hoshi et al., 1997b; Hoshi et al., 1996). Triple transgenic mouse models of Alzheimer’s disease, in addition to showing increased amyloid and phosphorylated tau deposits, also exhibit decreased fluorodeoxyglucose (FDG) uptake in brain (Nicholson et al., 2010). These findings are also compatible with the ability of ketone body metabolisms to bypass the inhibition of PDH and produce large amounts of acetyl CoA required to supply the Krebs cycle (Sato et al., 1995). These and other reports have led to the proposal that the amyloid cascade hypothesis be rejected (Herrup, 2015), although defenders of the amyloid hypothesis remain and propose that amyloid accumulation is a necessary accompaniment of the disease (Musiek and Holtzman, 2015).

Central to Alzheimer’s disease is the decrease in cerebral glucose use. Decreases in cerebral glucose metabolism occurs well before the clinical or pathological changes of Alzheimer’s disease (Blum-Degen et al., 1995; Cunnane et al., 2011; Hoyer et al., 1991). Inhibition of brain PDH has long been reported in the autopsy specimens from brains of patients with Alzheimer’s disease (Gibson et al., 1998). Indeed, intracerebral injection of streptozotocin, a drug that inhibits insulin secretion, leads to a decrease in insulin synthesis in brain (Grunblatt et al., 2007). Decreases in brain oxidative metabolism lead to altered processing of amyloid precursor protein, increased amyloid accumulation (Hoyer, 1996), and to neuronal death. These changes in brain nutrient metabolism, which precede either the clinical or pathological changes of the disease, suggest that decreased brain insulin sensitivity (Talbot et al., 2012; Willette et al.,

2015) and decreased brain energy production is an important factor in understanding the etiology of Alzheimer’s disease (Ding et al., 2013; Morgen and Frolich, 2015). Indeed, a deficit in brain energy metabolism alters the processing of brain APP (Gabuzda et al., 1994), suggesting the possibility that the accumulation of amyloid in the brains of patients with Alzheimer’s disease results from a deficit in cerebral energy metabolism. The accumulation of protein is not unique to Alzheimer’s disease, but occurs in other neurodegenerative conditions as reflected in the accumulation of α-synuclein in Parkinson’s disease and huntintin in Huntington’s disease. These observations suggest that the accumulation of amyloid in the brains of patients with Alzheimer’s disease is secondary to a primary defect in cerebral energy metabolism resulting from PDH inhibition due to a decrease in cerebral insulin sensitivity. There is mounting evidence suggesting that brain insulin resistance is the major factor in the etiology of Alzheimer’s disease (Carro and Torres-Aleman, 2004; Craft et al., 2012; de la Monte, 2012; Bomfim et al., 2012; Kleinridders et al., 2014; Talbot et al., 2012). A recent study of patients with mild Alzheimer’s dementia were compared with cognitively normal age-matched controls and were found to have a decrease in cerebral ^{18}F-fluorodeoxyglucose uptake but no decrease in cerebral metabolism of ^{11}C-acetoacetate (Castellano et al., 2015). These results suggest that in patients with mild cognitive impairment, perfusion with a ketone body can overcome the metabolic defect resulting from the brain’s inability to use glucose. Indeed Alzheimer’s disease has been called type 3 diabetes (Steen et al., 2005) due to the decrease in insulin and insulin-like growth factor signaling mechanisms in autopsy specimens of patients with Alzheimer’s disease.

The metabolism of ketone bodies can, therefore, correct this insulin deficiency in brain because the metabolism of ketone bodies mimics the metabolic effects of insulin by increasing the production of acetyl CoA for use in the Krebs cycle in the absence of normal PDH activity (Kashiwaya et al., 1997; Sato et al., 1995). This property of ketone body metabolism renders the administration of ketone bodies a rational method for the therapy of this disease (Figure **26.1**).

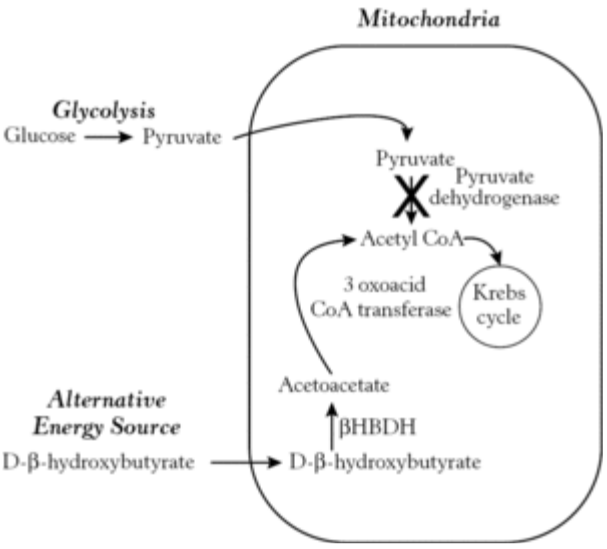

Figure 26.1
D-β-hydroxybutyrate metabolism produces acetyl CoA, which enters the Krebs, tricarboxylic acid cycle by an alternative pathway that does not require the usual path through pyruvate dehydrogenase (PDH).

In addition to insulin resistance, patients with Alzheimer’s disease also show multiple physiological signs indicative of free radical damage (Wang et al., 2013). The metabolism of ketone bodies can reduce free radical damage by reducing the free cytosolic [$NADP^+$]/[NADPH] ratio making it the lowest redox potential in the cell (Krebs, 1969). NADPH is the terminal destroyer of oxygen free radicals. Additionally, the β-hydroxybutyrate molecule itself inhibits histone deacetylase (HDAC). This inhibition of HDAC allows the acetyl groups on histones to remain in place so that the tightly packed structure can be relaxed and available to the FOXO3 transcription factors which leads to the transcription of the enzymes responsible for the destruction of ROS (Offermanns, 2006; Shimazu et al., 2013). The actual removal of the ROS is powered by NADPH of the free cytosolic [$NADP^+$]/[NADPH] ratio (Krebs and Veech, 1969).

Treatment

The hypothesis that amyloid accumulation is the central etiological factor leading to Alzheimer’s disease has led multiple pharmaceutical companies to develop monoclonal antibodies to removed amyloid. Active amyloid vaccine trials were suspended due to the development of meningoencephalitis (Schenk, 2002). Passive immunotherapeutics with two antibodies have failed to significantly

improve cognitive function or prevent progression but are now being tested in the early stage of the disease (Panza et al., 2014). Newer antibodies are currently being tested in asymptomatic individuals at risk of developing the disease, based on the amyloid β cascade hypothesis, in the hope that this approach will retard the development of clinically observable disease. It is fair to say that, to date, the results have been very disappointing (Prins and Scheltens, 2013).

An alternative treatment for Alzheimer’s disease has been developed based on the hypothesis that the disease results from a primary failure of the brain to develop both phosphorylation and redox energy. The therapy has been based on the observations that during starvation ketone bodies can replace glucose as the major metabolic fuel in brain (Cahill and Aoki, 1980; Owen et al., 1967). The detailed effects of the metabolism of ketone bodies were not well understood. A study was undertaken to explore the metabolic effects of ketone body metabolism in the working perfused rat heart (Kashiwaya et al., 1994; Sato et al., 1995). The working perfused heart provides the complete data needed on the effects on redox and phosphorylation states, O_2 consumption, and metabolic efficiency. Addition of ketone bodies to the glucose perfused heart resulted in a reduction of the mitochondrial NAD- couple, an increase in the ΔG’ of ATP, and a decrease in glucose use, indicating that the metabolism of ketone bodies replaced in large part the heart’s need for glucose to supply its metabolic energy (Sato et al., 1995).

More remarkably, the addition and metabolism of ketone bodies, like addition of insulin, increased the joules of hydraulic work put out by the heart per mole of O_2 consumed (Kashiwaya et al., 1994), demonstrating that either ketone bodies or insulin could improve the metabolic efficiency of the working heart. Moreover, ketone body metabolism can mimic the metabolic effects of insulin (Kashiwaya et al., 1994). This increase in the efficiency of hydraulic work of the heart induced by either ketone bodies or insulin indicated an increase in the efficiency of mitochondrial energy generation. That increase in mitochondrial energy generation could later be translated into an increased physiological performance in elite athletes or in disease states where metabolic energy generation is deficient.

A detailed examination of the metabolites of the Krebs tricarboxcylic acid cycle showed that addition of insulin to the working glucose-perfused heart increased acetyl CoA content ninefold, while addition of 4-mM ketone bodies increased acetyl CoA 15-fold. This very large increase in acetyl CoA in the case of insulin addition was caused by that hormone’s increased PDH activity, the enzymatic gateway to the Krebs cycle (Coore

et al., 1971; Taylor and Jungas, 1974; Taylor et al., 1975). The even larger increase in acetyl CoA caused by the metabolism of ketone bodies demonstrated that metabolism of ketone bodies could bypass the major metabolic block in insulin sensitivity. The metabolism of ketone bodies mimics the effect of insulin’s activation of PDH by producing acetyl CoA from the ketone body acetoacetate via the succinyl CoA transferase reaction (Sato et al., 1995). The metabolism of ketone bodies mimics a major metabolic effect of insulin (Kashiwaya et al., 1997) and could therefore overcome insulin resistance, which is a common factor in many disease (Scheuermann-Freestone et al., 2004; Zhai et al., 2011) or injury states (Li and Messina, 2009), including the brain (Talbot et al., 2012) of Alzheimer’s disease patients.

The Krebs cycle is the major energy-producing metabolic pathway, which results in the aerobic production of ATP by the complete oxidation of glucose. In brain, glucose is essentially the only energy-producing substrate under fed conditions. The entry of glucose into the Krebs cycle occurs through the production of acetyl CoA from pyruvate in a reaction catalyzed by PDH. The speed of that essential reaction is increased by insulin and decreased by loss of sensitivity to insulin. The variation in the speed of this reaction strongly suggests the loss of sensitivity of the brain’s PDH to insulin is the root cause of Alzheimer’s disease.

Other metabolic changes of importance also occur with addition of ketone bodies or insulin. The ratio of [isocitrate]/[α-ketoglutarate] is increased by both, indicating a reduction of the free NADP system (Krebs and Veech, 1969). The free mitochondrial $[NAD^+]$/[NADH] ratio is also reduced 3- to 10-fold by the addition of either ketone bodies or insulin. Also of major significance is the increase in the ratio of [fumarate]/[succinate], indicating an oxidation of Q as seen in the ratio of [Coenzyme Q]/[Coenzyme QH_2] (Bergman et al., 2010). The increase in the redox span between the free mitochondrial NAD and Q couples indicates an increase in the ΔG of ATP hydrolysis from -53 to -60 k*J* /mole in spite of a decrease in O_2 consumption from 18.5 to 16–17 μmol/min. An increase in the energy of ATP hydrolysis per O_2 consumed was observed with the addition of either ketone bodies or insulin (see Figures **26.2** and **26.3**) (Sato et al., 1995).

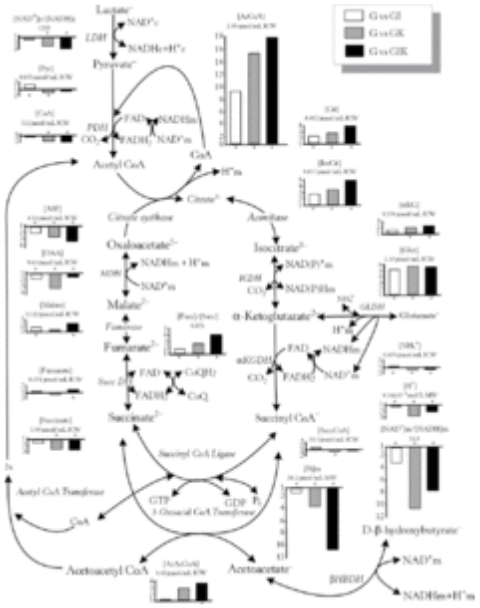

Figure 26.2
The study of perfused rat hearts treated with glucose, glucose + insulin, glucose + ketone (D-β-hydroxybutyrate), or glucose +insulin + ketone (D-β-hydroxybutyrate). The relevant pathways are shown along with concentration changes relative to just glucose.

Images are modified from Sato 1995 (Sato et al., 1995) originally drawn by Y. Kashiwaya.

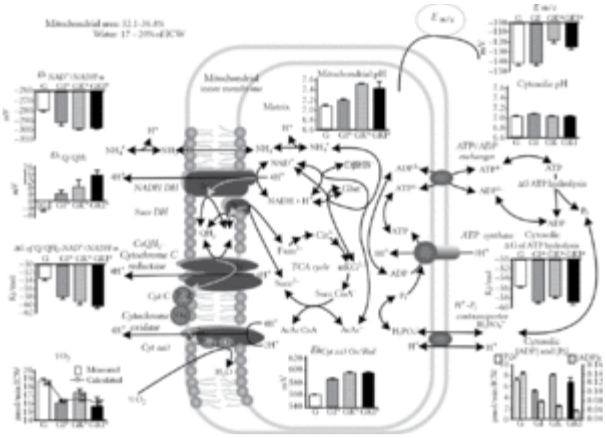

Figure 26.3
The study of perfused rat hearts treated with glucose, glucose + insulin, glucose + ketone (D-β-hydroxybutyrate), or glucose +insulin + ketones (D-β-hydroxybutyrate). The relevant pathways are shown along with the relevant measures of ΔG, Gibbs free energy calculated for the nonstandard concentrations, E, reduction potentials based on actual concentrations, VO2 is oxygen consumption in mL/kg/min.

Images are modified from Sato 1995 (Sato et al., 1995) originally drawn by Y. Kashiwaya.

What Forms of Ketone Bodies are Available?

Following the realization of the widespread effects of ketone body metabolism on the redox and phosphorylation states (Sato et al., 1995) and metabolic efficiency, it was recognized that therapeutic effects could result from the administration of ketone bodies (Cahill and Veech, 2003; Veech et al., 2001). During prolonged fasting (3 days) blood ketone body levels reach 5–7 mM (Cahill and Aoki, 1980). This blood level of ketone bodies results from the endogenous production of about 150 g of ketone bodies per day (Reichard et al., 1974). Therefore, to mimic the effects of the ketosis of starvation, about 150 g of ketone bodies, or about 1.5 moles, would be required to mimic the effects of starvation while maintaining safe levels (5–7 mM) of ketones. It is important to note that the minimum effective dose of ketone bodies in various disease states has not been established and may be much less than the 150 g per day produced during prolonged starvation.

Administration of ketone bodies as a simple acid or salt would present an unsafe load of either counter ion. Accordingly, examination of a variety of

alcohols was undertaken. *R*-1,3 butanediol was the alcohol chosen, because it was converted in the liver to ketone bodies (Mehlman and Veech, 1972). Thus, a monoester of D-β-hydroxybutyrate –*R*-1,3 butanediol monoester presents no other metabolite load than the ketone body.

Additionally, the oxidation state of the ketone body being administered needs to be considered. Ketone bodies are readily interconverted between the oxidized form, acetoacetate, and the reduced form, D-β-hydroxybutyrate.

$$\text{D–}\beta\text{–hydroxybutyrate} + \text{NAD}^+ \leftrightarrow \text{acetoacetate} + \text{NADH} + \text{H}^+$$

While both forms of the ketone body can be metabolized, the energetic effects are quite different. Acetoacetate can readily be used in the Langendorf perfused heart, which is a simpler model than the working perfused heart (Williamson and Krebs, 1961). In the working perfused rat heart, D-β-hydroxybutyrate can be used to power the beating heart effectively. When acetoacetate is substituted, the heart fails (Taegtmeyer et al., 1980), showing that the excessive oxidation of the mitochondria NAD couple produced by acetoacetate impairs cardiac energy production. Although acetoacetate is attractive because of its low cost, clearly it should be avoided as a supplement and the more expensive chiral molecule D-β-hydroxybutyrate should be considered instead.

R-1,3 butanediol is converted to D-β-hydroxybutyrate, the physiological form of the ketone body, which is first oxidized to acetoacetate and then activated by succinyl CoA transferase to acetoacetyl CoA and hence to 2 acetyl CoA s by thiolase (see Figure **26.1**). In contrast, *S* 1,3 butanediol is converted to L-β hydroxybutyrate, which is activated by ATP and CoA to form L-β-hydroxybutyryl CoA and further metabolized by the β fatty acid oxidation pathway (Lehninger & Greville, 1953). The metabolic fates of the D versus the L form of β-hydroxybutyrate are quite different, as shown in Figure **26.4**. Metabolism of one molecule of the physiological enantiomer D β-hydroxybutyrate consumes one molecule each of NAD^+, succinyl-CoA, CoASH, and CoQ and forms two molecules of acetyl-CoA, one molecule of fumarate, and one molecule each of the reduced forms of NAD^+ and coenzyme Q (QH_2). On the other hand, metabolism of the nonphysiological enantiomer, L β-hydroxybutyrate consumes two molecules of CoA-SH, one molecule of NAD^+, and one molecule of ATP and forms two molecules of acetyl-CoA and one molecule each of AMP and pyrophosphate as well as one molecule of the reduced form of NAD^+. A second molecule of ATP is also consumed to convert the AMP formed to ADP.

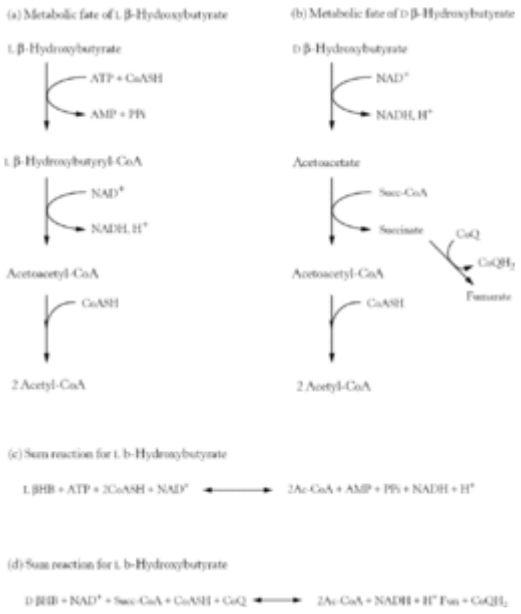

Figure 26.4
The metabolism and sum reactions for both D and L β-hydroxybutyrate.

Metabolism of the L form of β-hydroxybutyrate (A) uses two molecules of CoASH and one molecule each of ATP and NAD+ and forms 2 acetyl-CoAs and one molecule each of AMP, PPi, and reduced NAD+ (NADH, H+). Metabolism of the D form of β-hydroxybutyrate (B) on the other hand uses one molecule each of NAD+, succ-CoA, CoASH, and CoQ and produces two molecules of acetyl-CoA and one molecule each of fumarate and the reduced forms of NAD+ (NADN, H+), and CoQ (CoQH2). Sum reactions for each isomer are given in C and D.

In metabolizing mid-chain triglycerides (see Figure **26.5**), a reduced flavoprotein is produced in the β oxidation pathway, which results in a reduction of mitochondrial coenzyme Q, narrowing the redox span between mitochondrial NAD and Q and hence decreasing the energy available for ATP synthesis. This is in contrast to the increase in redox span that acompanies the metabolism of the physiological form of the ketone body, D-β-hydroxybutyrate (Sato et al., 1995).

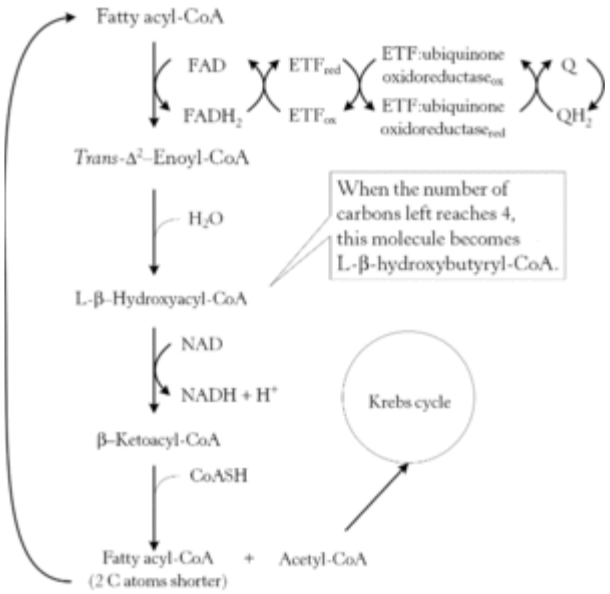

Figure 26.5
The beta-oxidation pathway of metabolizing fatty acids. The β fatty acid oxidation pathway produces 1 NADH and 1 flavoprotein compared with the two NADH’s produced by the oxidation of the physiologically normal D-β-hydroxybutyrate. Once you cycle down to the last two carbon atoms the terminal L-β-hydroxyacyl-CoA is L-β-hydroxybutyryl-CoA, not the D form of β-hydroxybutyrate.

It follows from the above, that the oxidized form of ketone body, acetoacetate, should not be included in esters for administration for the purpose of elevating ketone bodies because such solutions would oxidize the mitochondrial NAD couple and lower the energy available for the formation of ATP. Similarly, the use of racemic *R, S* 1.3 butanediol should not be used because the unphysiological *S* form undergoes β oxidation, producing mitochondrial flavoprotein, thus decreasing the oxidation of the Q couple, which results from the metabolism of the physiological *R*-3-hydroxybutyrate. Several studies using the acetoacetate and racemic 1,3 butanediol ester have appeared (D’Agostino, 2013; Desrochers et al., 1995). The effects of these ketone ester formulations would be quite different from those produced by the D-β-hydroxybutyrate–*R*-1, 3 butanediol monoester.

Evidence presented here suggests that Alzheimer’s disease results from a deficit in cerebral energy generation, primarily due to a loss of insulin sensitivity in brain, and that amyloid accumulation results from this decrease in cerebral metabolic energy. The primary therapeutic target

would therefore become not the removal of amyloid but the overcoming of the block of cerebral metabolic energy production caused by cerebral insulin resistance. This could be achieved by (1) feeding a therapeutic amount of D-β-hydroxybutyrate–*R* 1,3 butanediol monoester, producing acetyl CoA without requiring the activity of brain PDH (Kashiwaya et al., 2013; Newport et al., 2015). This approach has decreased amyloid and phosphorylated tau in the brains of triple transgenic mice and improved cognitive performance. In a single human subject, behavioral improvement on feeding ketone has been noted.

Alternatively, increasing the brain’s concentration of insulin by introducing insulin into brain through intranasal administration of insulin has been reported. This therapy also has proven successful in treating Alzheimer’s disease in a limited number of cases. Cerebrospinal fluid insulin levels were shown to be significantly lower in patients with Alzheimer’s than normal controls (Craft et al., 1998). The olfactory lobe contains the highest concentration of insulin receptors of any brain area (Kleinridders et al., 2014). Intranasal administration of large doses of insulin improve cognitive performance in patients with early cognitive impairment due to Alzheimer’s disease (Reger et al., 2008).

Ketone bodies mimic the metabolic effects of insulin. They increase the energy of ATP hydrolysis, decrease free radical damage, and increase the transcription of antioxidant enzymes by inhibiting histone deacetylase (Shimazu et al., 2013; Veech, 2014). In the genetic mouse model of early-onset Alzheimer’s disease, feeding mice ketone esters resulted in a decrease in brain amyloid and phosphorylated tau accumulation as well as improvement in cognitive function (Kashiwaya et al., 2013). Feeding ketone ester to a patient with advanced Alzheimer’s disease improved his behavior and cognitive function (Newport et al., 2015). These results support the need for larger clinical trials of ketone esters in the treatment of Alzheimer’s disease and other diseases where insulin resistance is a major etiological factor.

References

Alexander, P., and Stacey, K.A. (1959). Cross-linking of deoxyribonucleic acid in sperm heads by ionizing radiations. Nature 184, 958–960.

Alzheimer, A. (1907). Uber eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift fur Psychiatrie und physchish-Gerichtliche Medizin 64, 146–148.

Bergman, C., Kashiwaya, Y., and Veech, R.L. (2010). The effect of pH and free Mg2+ on ATP linked enzymes and the calculation of Gibbs free energy of ATP hydrolysis. J Phys Chem B 114, 16137–16146.

Biessels, G.J., and Reagan, L.P. (2015). Hippocampal insulin resistance and cognitive dysfunction. Nat Rev Neurosci 16(11), 660–671.

Blum-Degen, D., Frolich, L., Hoyer, S., and Riederer, P. (1995). Altered regulation of brain glucose metabolism as a cause of neurodegenerative disorders? J Neural Transm Suppl 46, 139–147, 139–147.

Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., et al. (2012). An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer’s disease- associated Abeta oligomers. J Clin Invest122, 1339–1353.

Cahill, G.F., Jr., and Aoki, T.T. (1980). Alternate fuel utilization in brain. In Cerebral metabolism and neural function, J.V. Passonneau, R.A. Hawkins, W.D. Lust, and F.A. Welsh, eds. (Baltimore: Williams & Wilkins), pp. 234–242.

Cahill, G.F., Jr., and Veech, R.L. (2003). Ketoacids? Good medicine? Trans Am Clin Climatol Assoc 114, 149–161; discussion 162–163, 149–161.

Carro, E., and Torres-Aleman, I. (2004). The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer’s disease. Eur J of Pharmacol 490, 127–133.

Castellano, C.A., Nugent, S., Paquet, N., Tremblay, S., Bocti, C., Lacombe, G., Imbeault, H., Turcotte, E., Fulop, T., and Cunnane, S.C. (2015). Lower brain 18F-fluorodeoxyglucose uptake but normal 11C-acetoacetate metabolism in mild Alzheimer’s disease dementia. J Alzheimers Dis 43, 1343–1353.

Coore, H.G., Denton, R.M., Martin, B.R., and Randle, P.J. (1971). Regulation of adipose tissue pyruvate dehydrogenase by insulin and other hormones. Biochem J 125, 115–127.

Cotman, C.W., Berchtold, N.C., and Christie, L.A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 30, 464–472.

Craft, S., Cholerton, B., and Baker, L.D. (2012). Insulin and Alzheimer’s disease: untangling the web. Journal of Alzheimer’s Disease: JAD 33 Suppl 1, S263–275.

Craft, S., Peskind, E., Schwartz, M.W., Schellenberg, G.D., Raskind, M., and Porte, D., Jr. (1998). Cerebrospinal fluid and plasma insulin levels in Alzheimer’s disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 50, 164–168.

Cunnane, S., Nugent, S., Roy, M., Courchesne-Loyer, A., Croteau, E., Tremblay, S., Castellano, A., Pifferi, F., Bocti, C., Paquet, N., et al. (2011). Brain fuel metabolism, aging, and Alzheimer’s disease. Nutrition 27, 3–20.

D’Agostino, D. P., Pilla, R., Held, H. E., Landon, C. S., Puchowicz, M., Brunengraber, H., … Dean, J. B. (2013). Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. American Journal of Physiology – Regulatory, Integrative and Comparative Physiology, 304(10), R829–R836.

de la Monte, S.M. (2012). Brain insulin resistance and deficiency as therapeutic targets in Alzheimer’s disease. Curr Alzheimer Res 9, 35–66.

DeKosky, S.T., Ikonomovic, M.D., and Gandy, S. (2010). Traumatic brain injury: football, warfare, and long-term effects. N Engl J Med 363, 1293–1296.

Dekosky, S.T., Blennow, K., Ikonomovic, M.D., and Gandy, S. (2013). Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. Nat Rev Neurol 9, 192–200.

Desrochers, S., Quinze, K., Dugas, H., Dubreuil, P., Bomont, C., David, F., Agarwal, K.C., Kumar, A., Soloviev, M.V., Powers, L., et al. (1995). (R,S) 1,3 butandiol acetoacetate esters, potential alternates to lipid emulsions for total parenteral nutrition. J Nutr Biochem 6, 109–116.

Ding, F., Yao, J., Rettberg, J.R., Chen, S., and Brinton, R.D. (2013). Early decline in glucose transport and metabolism precedes shift to ketogenic system in female aging and Alzheimer’s mouse brain: implication for bioenergetic intervention. PloS One 8, e79977.

Evans, D.A., Funkenstein, H.H., Albert, M.S., Scherr, P.A., Cook, N.R., Chown, M.J., Hebert, L.E., Hennekens, C.H., and Taylor, J.O. (1989). Prevalence of Alzheimer’s disease in a community population of older persons. Higher than previously reported [see comments]. JAMA 262, 2551–2556.

Gabuzda, D., Busciglio, J., Chen, L.B., Matsudaira, P., and Yankner, B.A. (1994). Inhibition of energy metabolism alters the processing of amyloid precursor protein and induces a potentially amyloidogenic derivative. J Biol Chem 269, 13623–13628.

Gibson, G.E., Sheu, K.F., and Blass, J.P. (1998). Abnormalities of mitochondrial enzymes in Alzheimer disease. J Neural Transm 105, 855–870.

Grunblatt, E., Salkovic-Petrisic, M., Osmanovic, J., Riederer, P., and Hoyer, S. (2007). Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. J Neurochem 101, 757–770.

Halagappa, V.K., Guo, Z., Pearson, M., Matsuoka, Y., Cutler, R.G., Laferla, F.M., and 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.

Harman, D. (1956). Aging: a theory based on free radical and radiation chemistry. J Gerontol 11, 298–300.1

Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. Nat Neurosci 8, 794–799.

Hoshi, M., Takashima, A., Noguchi, K., Murayama, M., Sato, M., Kondo, S., Saitoh, Y., Ishiguro, K., Hoshino, T., and Imahori, K. (1996). Regulation of mitochondrial pyruvate dehydrogenase activity by tau protein kinase I/glycogen synthase kinase 3beta in brain. Proc Natl Acad Sci USA 93, 2719–2723.

Hoshi, M., Takashima, A., Murayama, M., Yasutake, K., Yoshida, N., Ishiguro, K., Hoshino, T., and Imahori, K. (1997a). Nontoxic amyloid á peptide 1-42 suppresses acetylcholine synthesis. J Biol Chem 272, 2038–2041.

Hoshi, M., Takashima, A., Murayama, M., Yasutake, K., Yoshida, N., Ishiguro, K., Hoshino, T., and Imahori, K. (1997b). Nontoxic amyloid beta peptide 1-42 suppresses acetylcholine synthesis. Possible role in cholinergic dysfunction in Alzheimer’s disease. J Biol Chem 272, 2038–2041.

Hoyer, S. (1991). Abnormalities of glucose metabolism in Alzheimer’s disease. Ann N Y Acad Sci 640, 53–58.

Hoyer, S. (1996). Oxidative metabolism deficiencies in brains of patients with Alzheimer’s disease. Acta Neurol Scand Suppl 165, 18–24, 18–24.

Hoyer, S., Nitsch, R., and Oesterreich, K. (1991). Predominant abnormality in cerebral glucose utilization in late-onset dementia of the Alzheimer type: a cross-sectional comparison against advanced late-onset

and incipient early-onset cases. J Neural Transm Park Dis Dement Sect 3, 1–14.

Johnson-Wood, K., Lee, M., Motter, R., Hu, K., Gordon, G., Barbour, R., Khan, K., Gordon, M., Tan, H., Games, D., et al. (1997). Amyloid precursor protein processing and A beta42 deposition in a transgenic mouse model of Alzheimer disease. Proc Natl Acad Sci USA 94, 1550–1555.

Josephs, K.A., Whitwell, J.L., Ahmed, Z., Shiung, M.M., Weigand, S.D., Knopman, D.S., Boeve, B.F., Parisi, J.E., Petersen, R.C., Dickson, D.W., et al. (2008). Beta-amyloid burden is not associated with rates of brain atrophy. Ann Neurol 63, 204–212.

Kashiwaya, Y., Sato, K., Tsuchiya, N., Thomas, S., Fell, D.A., Veech, R.L., and Passonneau, J.V. (1994). Control of glucose utilization in working perfused rat heart. J Biol Chem 269, 25502–25514.

Kashiwaya, Y., King, M.T., and Veech, R.L. (1997). Substrate signaling by insulin: a ketone bodies ratio mimics insulin action in heart. Am J Cardiol 80, 50A–64A.

Kashiwaya, Y., Takeshima, T., Mori, N., Nakashima, K., Clarke, K., and Veech, R.L. (2000). D-beta -Hydroxybutyrate protects neurons in models of Alzheimer’s and Parkinson’s disease. Proc Natl Acad Sci USA 97, 5440–5444.

Kashiwaya, Y., Bergman, C., Lee, J.H., Wan, R., Todd King, M., Mughal, M.R., Okun, E., Clarke, K., Mattson, M.P., and Veech, R.L. (2013). A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer’s disease. Neurobiol Aging 34, 1530–1539.

Kempf, S.J., Azimzadeh, O., Atkinson, M.J., and Tapio, S. (2013). Long-term effects of ionising radiation on the brain: cause for concern? Radiat Environ Biophys 52, 5–16.

Kleinridders, A., Ferris, H.A., Cai, W., and Kahn, C.R. (2014). Insulin action in brain regulates systemic metabolism and brain function. Diabetes 63, 2232–2243.

Krebs, H.A., and Veech, R.L. (1969). Pyridine nucleotide interrelations. In The Energy Level and Metabolic Control in Mitochondria, S. Papa, Tager, J.M., Quagliariello, E., & Slater, E.C., eds. (Bari, Italy: Adriatica Editrice), pp. 329–383.

Kuusisto, J., Koivisto, K., Mykkanen, L., Helkala, F.L., Vanhunen, M., Kervinen, K., Kesaniemi, Y.A., Riekkinen, P.J., and Laakso, M. (1997). Association between features of the insulin resistance syndrome and Alzheimer’s disease independently of apolipoprotein E4 phenotype: cross sectional population based study. Brit Med J 315, 1045–1049.

Lehninger, A.L., and Greville, G.D. (1953). The enzymatic oxidation of d and l b hydroxybutyrate. Biochem Biophys Acta 12, 188–202.

Li, L., and Messina, J.L. (2009). Acute insulin resistance following injury. Trends Endocrinol Metab 20, 429–435.

Li, L., Wang, W., Welford, S., Zhang, T., Wang, X., and Zhu, X. (2014). Ionizing radiation causes increased tau phosphorylation in primary neurons. J Neurochem 131, 86–93.

Martin, E.S., Martin, S.E., Edelsohn, L., and Borgaonkar, D.S. (1997). Studies in a large family with late-onset Alzheimer disease (LOAD). Alzheimer Dis Assoc Disord 11, 163–170.

Mehlman, M.A., and Veech, R.L. (1972). Redox and phosphorylation states and metabolite concentrations in frozen clamped livers of rats fed diets containing 1,3- butanediol and DL-carnitine. J Nutr 102, 45–51.

Morgen, K., and Frolich, L. (2015). The metabolism hypothesis of Alzheimer’s disease: from the concept of central insulin resistance and associated consequences to insulin therapy. J Neural Transm 122, 499–504.

Mouton, P.R., Chachich, M.E., Quigley, C., Spangler, E., and Ingram, D.K. (2009). Caloric restriction attenuates amyloid deposition in middle-aged dtg APP/PS1 mice. Neurosci Lett 464(3), 184–187.

Musiek, E.S., and Holtzman, D.M. (2015). Three dimensions of the amyloid hypothesis: time, space and ‘wingmen’. Nat Neurosci 18, 800–806.

Naj, A.C., Jun, G., Reitz, C., Kunkle, B.W., Perry, W., Park, Y.S., Beecham, G.W., Rajbhandary, R.A., Hamilton-Nelson, K.L., Wang, L.S., et al. (2014). Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA Neurol 71, 1394–1404.

Newport, M.T., VanItallie, T.B., Kashiwaya, Y., King, M.T., and Veech, R.L. (2015). A new way to produce hyperketonemia: Use of ketone ester in a case of Alzheimer’s disease. Alzheimers Dement 11, 99–103.

Nicholson, R.M., Kusne, Y., Nowak, L.A., LaFerla, F.M., Reiman, E.M., and Valla, J. (2010). Regional cerebral glucose uptake in the 3xTG model of Alzheimer’s disease highlights common regional vulnerability across AD mouse models. Brain Res 1347, 179–185.

Offermanns, S. (2006). The nicotinic acid receptor GPR109A (HM74A or PUMA-G) as a new therapeutic target. Trends Pharmacol Sci 27, 384–390.

Ott, A., Stolk, R.P., Hofman, A., van Harskamp, F., Grobbee, D.E., and Breteler, M.M. (1996). Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 39, 1392–1397.

Owen, O.E., Morgan, A.P., Kemp, H.G., Sullivan, J.M., Herrera, M.G., and Cahill, G.F. (1967). Brain metabolism during fasting. J Clin Invest 46, 1589–1595.

Panza, F., Logroscino, G., Imbimbo, B.P., and Solfrizzi, V. (2014). Is there still any hope for amyloid-based immunotherapy for Alzheimer’s disease? Curr Opin Psychiatry 27, 128–137.

Prins, N.D., and Scheltens, P. (2013). Treating Alzheimer’s disease with monoclonal antibodies: current status and outlook for the future. Alzheimers Res Ther 5, 56.

Reaven, G.M., Thompson, L.W., Nahum, D., and Haskins, E. (1990). Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care 13, 16–21.

Reger, M.A., Watson, G.S., Green, P.S., Wilkinson, C.W., Baker, L.D., Cholerton, B., Fishel, M.A., Plymate, S.R., Breitner, J.C., DeGroodt, W., et al. (2008). Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 70, 440–448.

Reichard, G.A., Owen, O.E., Haff, A.C., Paul, P., and Bortz, W.M. (1974). Ketone-body production and oxidation in fasting obese humans. J Clin Invest 53, 508–515.

Riley, P.A. (1994). Free radicals in biology: oxidative stress and the effects of ionizing radiation. Int J Radiat Biol 65, 27–33.

Roses, A.D. (2006). On the discovery of the genetic association of apolipoprotein E genotypes and common late-onset Alzheimer disease. J Alzheimers Dis 9, 361–366.

Sato, K., Kashiwaya, Y., Keon, C.A., Tsuchiya, N., King, M.T., Radda, G.K., Chance, B., Clarke, K., and Veech, R.L. (1995). Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J 9, 651–658.

Schenk, D. (2002). Amyloid-beta immunotherapy for Alzheimer’s disease: the end of the beginning. Nat Rev Neurosci 3, 824–828.

Scheuermann-Freestone, M., Neubauer, S., and Clarke, K. (2004). Abnormal cardiac muscle function in heart failure is related to insulin resistance. Cardiovasc J S Afr 15, S12.

Selkoe, D.J. (1997). Alzheimer’s disease: genotypes, phenotypes, and treatments. Science 275, 630–631.

Selkoe, D.J. (2001). Alzheimer’s disease: genes, proteins, and therapy. Physiol Rev 81, 741–766.

Shimazu, T., Hirschey, M.D., Newman, J., He, W., Shirakawa, K., Le Moan, N., Grueter, C.A., Lim, H., Saunders, L.R., Stevens, R.D., et al. (2013). Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 339, 211–214.

Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., and de la Monte, S.M. (2005). Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer’s disease: is this type 3 diabetes? J Alzheimers Dis 7, 63–80.

Strittmatter, W.J., and Roses, A.D. (1995). Apolipoprotein E and Alzheimer disease. Proc Natl Acad Sci USA 92, 4725–4727.

Szilard, L. (1959). On the nature of the aging process. Proc Natl Acad Sci USA 45, 30–45.

Taegtmeyer, H., Hems, R., and Krebs, H.A. (1980). Utilization of energy-providing substrates in the isolated working rat heart. Biochem J 186, 701–711.

Talbot, K., Wang, H.Y., Kazi, H., Han, L.Y., Bakshi, K.P., Stucky, A., Fuino, R.L., Kawaguchi, K.R., Samoyedny, A.J., Wilson, R.S., et al. (2012). Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 122, 1316–1338.

Taylor, S.I., and Jungas, R.L. (1974). Regulation of lipogenesis in adipose tissue: the significance of the activation of pyruvate dehydrogenase by insulin. Arch Biochem Biophys 164, 12–19.

Taylor, S.I., Mukherjee, C., and Jungas, R.L. (1975). Regulation of pyruvate dehydrogenase in isolated rat liver mitochondria. Effects of octanoate, oxidation-reduction state, and adenosine triphosphate to adenosine diphosphate ratio. J Biol Chem 250, 2028–2035.

Thies, W., and Bleiler, L. (2013). 2013 Alzheimer’s disease facts and figures. Alzheimers Dement 9, 208–245.

Veech, R.L. (2014). Ketone ester effects on metabolism and transcription. J Lipid Res 55, 2004–2008.

Veech, R.L., Chance, B., Kashiwaya, Y., Lardy, H.A., and Cahill, G.F., Jr. (2001). Ketone bodies, potential therapeutic uses. IUBMB Life 51, 241–247.

Wang, X., Wang, W., Li, L., Perry, G., Lee, H.G., and Zhu, X. (2013). Oxidative stress and mitochondrial dysfunction in Alzheimer’s disease. Biochim Biophys Acta 1842(8), 1240–1247.

Willette, A.A., Bendlin, B.B., Starks, E.J., Birdsill, A.C., Johnson, S.C., Christian, B.T., Okonkwo, O.C., La Rue, A., Hermann, B.P., Koscik, R.L., et al. (2015). Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer disease. JAMA Neurology 72(9), 1013–1020.

Williamson, J.R., and Krebs, H.A. (1961). Acetoacetate as fuel of respiration in the perfused rat heart. Biochem J 80, 540–547.

Xu, W., Qiu, C., Gatz, M., Pedersen, N.L., Johansson, B., and Fratiglioni, L. (2009). Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Diabetes 58, 71–77.

Zhai, L., Ballinger, S.W., and Messina, J.L. (2011). Role of reactive oxygen species in injury-induced insulin resistance. Mol Endocrinol 25, 492–502.