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REVIEW – DOSSIER		OPEN ACCESS

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Ketones and brain development: Implications for correcting deteriorating brain glucose metabolism during aging

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Abstract – Brain energy metabolism in Alzheimer's disease (AD) is characterized mainly by temporo-parietal glucose hypometabolism. This pattern has been widely viewed as a consequence of the disease, *i.e.* deteriorating neuronal function leading to lower demand for glucose. This review will address deteriorating glucose metabolism as a problem specific to glucose and one that precedes AD. Hence, ketones and medium chain fatty acids (MCFA) could be an alternative source of energy for the aging brain that could compensate for low brain glucose uptake. MCFA in the form of dietary medium chain triglycerides (MCT) have a long history in clinical nutrition and are widely regarded as safe by government regulatory agencies. The importance of ketones in meeting the high energy and anabolic requirements of the infant brain suggest they may be able to contribute in the same way in the aging brain. Clinical studies suggest that ketogenesis from MCT may be able to bypass the increasing risk of insufficient glucose uptake or metabolism in the aging brain sufficiently to have positive effects on cognition.

Keywords: Brain energy metabolism / Alzheimer's disease / medium chain triglycerides / ketones / aging

Résumé – Cétones et développement du cerveau : applications en vue de compenser la détérioration du métabolisme cérébral du glucose associée au vieillissement. Le métabolisme énergétique du cerveau dans la maladie d'Alzheimer (MA) se caractérise principalement par un hypométabolisme du glucose dans les régions temporopariétales. Ce patron métabolique a souvent été considéré comme une conséquence de la maladie *c.-à-d.* la détérioration de la fonction neuronale mène à une demande plus faible en glucose. Cette revue de littérature portera sur la détérioration du métabolisme cérébral comme un problème spécifique au glucose précédant le développement de la MA. Dans ce contexte, les cétones et les acides gras à chaîne moyenne (AGCM) pourraient être une source d'énergie alternative pour le cerveau vieillissant en compensant la réduction du glucose. Historiquement, les AGCM sous la forme de triglycérides à chaîne moyenne (MCT) alimentaires sont depuis longtemps utilisés en nutrition clinique et sont considérés sécuritaires par les différents organismes de réglementation gouvernementaux. L'importance des cétones pour répondre aux besoins élevés en énergie et en anabolisants du cerveau chez le nourrisson suggère que ceux-ci pourraient être en mesure d'aider le cerveau vieillissant. Des études cliniques ont montrées que la cétogenèse par les MCT permettait de compenser la réduction de la capture et/ou du métabolisme du glucose cérébral associée au vieillissement et ainsi d'apporter des bénéfices cognitifs.

Mots clés : Métabolisme énergétique cérébral / maladie d'Alzheimer / triglycérides à chaîne moyenne / cétones / vieillissement

1 Introduction

A pattern of low brain glucose uptake in the parietal and temporal cortex has long been associated with Alzheimer's disease (AD). This pattern has been widely viewed as a *consequence* of the disease, *i.e.* deteriorating neuronal function leads to lower demand for glucose and, hence, lower brain glucose uptake. However, three lines of evidence suggest that low brain uptake of glucose is not just a consequence of AD, but may also *contribute* to its onset (Henderson *et al.*, 2009; Jagust and Landau, 2012; Krikorian *et al.*, 2012; Nugent *et al.*, 2014b;

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Reiman *et al.*, 1996, 2004): first, low glucose uptake can clearly be present pre-symptomatically, *i.e.* before measurable cognitive decline, in regions of the brain associated with low glucose uptake in AD. Second, if low regional brain glucose uptake in AD were uniquely a consequence of failing neuronal function then the uptake of ketones, which are the brain's main alternative fuel to glucose, should also be similarly defective in the same regions but this is not the case. Third, clinical studies show that providing an alternative fuel to glucose such as ketones results in a modest improvement in cognition in AD and in other neurological conditions. These lines of evidence do not refute the view that deteriorating brain glucose uptake can be the consequence of cognitive decline in AD. However, they strongly suggest that deteriorating brain glucose uptake may be specific to glucose and may also contribute to AD. Furthermore, they raise the possibility that a strategy to correct or bypass this problem using ketones could be therapeutically useful in AD.

This review will address these points and discuss what can be learned from the importance of ketones and medium chain fatty acids (MCFA) in infant brain development as a basis for using MCFA therapeutically to stimulate ketogenesis in order to compensate for or bypass deteriorating brain glucose and thereby delay the risk or onset of AD.

2 Lower pre-symptomatic brain glucose uptake

Lower pre-symptomatic brain glucose uptake refers to brain glucose uptake that is lower in individuals that are at risk of AD but do not yet have any objective clinical evidence of lower performance on cognitive tests. Brain glucose uptake is invariably measured using positron emission tomography (PET) with the tracer 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG). Brain FDG uptake may be reported as a statistical (relative) difference or may be quantified in absolute terms such as "cerebral metabolic rate of glucose" (CMRg; μmol/100 g/min); in both cases, these values are compared to those of a control group which should be matched as closely as possible, particularly in age and education. Brain glucose uptake (transport) and metabolism (glycolysis) are both defective in AD (Cunnane *et al.*, 2011). However, one limitation of PET-FDG is that it only permits detection of a problem with glucose *uptake* but not the possible presence of a problem in glycolysis.

Carriers of the Presenilin-1 mutation are essentially guaranteed to get familial or early onset AD starting typically in their mid-late forties. One report shows that Presenilin-1 carriers with normal cognitive scores in their mid-thirties already have significantly lower glucose uptake in the right thalamus (Scholl *et al.*, 2011). Presenilin-1 carriers represent a key example of a population at very high risk of AD in whom regional brain glucose uptake is defective 10–15 years before the expected onset of AD. Carriers of the apolipoprotein E4 allele also have higher risk of sporadic or late-onset AD but the risk of AD development is not nearly as high as Presenilin-1 carriers (Corder *et al.*, 1993). Young adults in their 30 s and who are homozygous for the e4 allele of apolipoprotein E still have normal cognition but have lower brain glucose uptake in regions typically affected in AD (Reiman *et al.*, 2004). Maternal family history is a risk factor for developing AD. Older adults between the ages of fifty and eighty years with a maternal family history of AD have shown glucose hypometabolism, consistent with the disease, despite remaining cognitively normal (Mosconi *et al.*, 2007). In addition to genetic mutations, polymorphisms or familial risk factors, lifestyle factors such as insulin resistance and/or type 2 diabetes also play an important role in the risk of developing AD. Adults in their seventies with type 2 diabetes have an abnormal pattern of brain glucose uptake despite normal cognitive scores (Baker *et al.*, 2011). Young women with mild insulin resistance due to polycystic ovary syndrome have 9–14% lower glucose uptake in parts of the temporal and parietal cortex, regions which are also affected by low glucose uptake in early AD (Castellano *et al.*, 2015a).

Metabolically healthy older persons with normal cognitive scores also have an altered pattern of brain glucose uptake, but this altered pattern affects almost exclusively the frontal cortex and caudate which is not a pattern typical of that seen in AD (Castellano *et al.*, 2015b; Nugent *et al.*, 2014a, 2014b). Aging is clearly associated with a higher risk of AD, but it is not clear that it is aging *per se* which is responsible for that heightened risk; pre-symptomatic changes in the regulation of glucose metabolism that commonly accompany aging may also play a role (Nugent *et al.*, 2015).

3 Push-pull: two strategies of the brain to take up fuel

Ketones (or ketone bodies) refer mainly to β-hydroxybutyrate and acetoacetate. Brain ketone uptake is via the monocarboxylic acid transporter which is distinct from the glucose transporters GLUTs (Morris, 2005; Pierre and Pellerin, 2005). Ketone access to the citric acid (Krebs') cycle is direct, via acetyl-CoA rather than through glycolysis (Mamelak, 2012; Veech *et al.*, 2001). Brain glucose uptake is driven primarily by brain activity which consumes glucose and transiently lowers glucose concentrations in the actived region. This in turn stimulates brain glucose uptake in the actived region in order to perpetuate further neuronal activation. Neuronal activation that stimulates glucose uptake may be considered as a *'pull'* strategy to replace glucose that has been consumed (Fig. 1). In contrast, several studies show that brain ketone uptake increases in direct proportion to the rise in blood ketone concentrations, irrespective of brain activity (Blomqvist *et al.*, 1995, 2002; Cunnane *et al.*, 2011; Nugent *et al.*, 2014b). Hence, brain ketone uptake may considered as a *'push'* strategy because it is driven, not by ketone metabolism in the brain cell, but by blood ketone concentrations. Indeed, it is logical that brain ketone uptake respond not to brain activity but to ketone *supply* because ketones are the back-up fuel, *i.e.* under normal circumstances, the presence of ketones in the blood is due to low insulin which is commensurate with low glucose, so it is necessary for them to be able to access the brain rapidly in order to avoid a crisis in brain energy supply. Hence, ketones are actually the brain's *preferred* fuel but are not normally produced in amounts exceeding about 3%

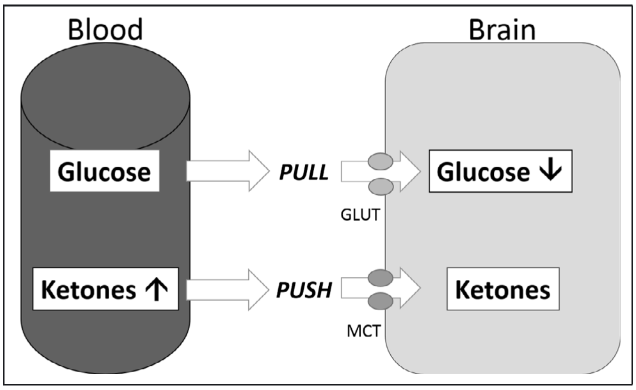

Fig. 1. Push-pull: two distinct strategies to supply the brain with energy substrates. Glucose is the brain's main fuel and is taken up by the brain in relation to demand. Hence, this is a "pull" strategy because glucose is pulled into the cell following neuronal activation and the subsequent decrease in neuronal glucose concentrations. Ketones are the brain's main alternate fuel to glucose and are taken up by the brain in relation to their presence in blood. Hence, this is a "push" strategy because ketones are pushed into the brain in direct proportion to their concentrations in the blood.

of total brain energy requirements; however, when they are produced, it is because they are needed to replace decreasing glucose supply.

4 Normal brain ketone uptake in AD

As the main alternative brain fuel to glucose, ketones provide an opportunity to assess the specificity of the metabolic problem related to brain glucose uptake in AD. Hence, if the glucose problem in AD or in conditions associated with a higher risk of AD were to be specific to glucose, brain ketone uptake should be normal in those conditions. While, if the problem were not specific to glucose, brain ketone uptake should be lower in conditions associated with AD and should show a similar regional pattern to that of glucose. Prior to the development of PET, brain uptake of metabolites was assessed by measuring arterio-venous differences which showed that ketones could provide up to two-thirds of the adult human brain's energy requirements (Owen *et al.*, 1967). The arterio-venous difference technique also showed that overall brain glucose uptake was lower in moderate AD but that ketone uptake was normal (Lying-Tunell *et al.*, 1981; Ogawa *et al.*, 1996). However, the arterio-venous difference technique does not permit a regional assessment of brain fuel metabolism. Using PET with the ketone tracer – carbon-11 acetoacetate, we have since confirmed the observations made by measuring arterio-venous differences which showed that brain glucose but not brain ketone uptake was lower in mild AD patients (Castellano *et al.*, 2015b). The two methods therefore agree that brain ketone uptake is still normal but that there is a specific pattern of defective brain glucose uptake in mild to moderate AD. We interpret these results as indicating that the problem of brain fuel uptake in AD is specific to glucose. Nevertheless, the conditions in which brain ketone uptake have been reported have always been when ketonemia is < 0.5 mM, *i.e.* when ketones are a relatively minor brain fuel supplying at most ~3% of brain energy requirements. It remains to be seen as to whether brain ketone uptake can be increased in older persons or in AD during mild ketosis, *i.e.* when more ketones are being produced following ingestion of MCFA and supplying > 10–15% of brain energy requirements, which would be closer to the therapeutic range necessary to compensate for impaired brain glucose uptake (Cunnane *et al.*, 2011).

5 Cognitive benefits of increasing brain ketone supply

Since brain ketone uptake is still normal in mild to moderate AD and the problem of low brain glucose uptake appears to be contributing to declining cognition in AD, it is reasonable to hypothesize that providing the brain with more ketones may delay any further cognitive decline. This hypothesis has been supported by results from acute and chronic studies in AD patients (Henderson *et al.*, 2009; Newport *et al.*, 2015; Reger *et al.*, 2004) and in the prodromal condition to AD – mild cognitive impairment (Krikorian *et al.*, 2012). Other trials with ketogenic supplements in AD are ongoing (https://clinicaltrials.gov/ct2/results?term=ketones+Alzheimer%27s\&Search=Search). Conditions involving acute or long-term cognitive problems including post-insulin hypoglycemia (Page *et al.*, 2009) and epilepsy (Cross, 2009; Neal *et al.*, 2008) also respond to a ketogenic diet or supplement.

One of the reasons that type 2 diabetes is such an important risk factor for AD may be due to insulin resistance. The brain has long been thought to function independently of insulin, but this is now being challenged. Insulin resistance not only affects glucose uptake by peripheral tissues but it also blocks ketogenesis, thereby limiting production of ketones to be taken up by the brain. Indeed, if the insulin resistance of type 2 diabetes in some way impairs brain glucose metabolism, brain energy supply is in fact in double jeopardy because insulin excess also blocks ketogenesis from long chain fatty acids stored in adipose tissue thereby restricted access not just of the brain's primary fuel (glucose) but its main back-up fuel (ketones) as well. One potential solution is that ketogenesis from MCFA appears to be independent of insulin, in which case a ketogenic MCFA supplement should still be able to supply the brain with ketones despite the presence of insulin resistance or type 2 diabetes. This is an active area of research.

6 Ketones and infant brain development

Raising plasma ketones is commonly viewed as risky, primarily because ketosis is associated with uncontrolled type 1 diabetes, *i.e.* an acute and severe absence of insulin. However, *pathological ketosis* needs to be distinguished from *nutritional ketosis*: the former is associated with metabolic ketoacidosis, *i.e.* plasma ketones exceeding 15 mM, which is medically serious condition requiring rapid treatment. In contrast, the latter is associated with plasma ketones below 5 mM and can be safely induced by short- or long-term dietary modification. The very high fat ketogenic diet induces nutritional, not pathological ketosis. It has been used for nearly 100 years as a standard-of-care for intractable childhood epilepsy and is rarely associated with serious side-effects despite producing plasma ketones averaging 2–5 mM for periods commonly exceeding 2 years. Its mechanism of action is still poorly understood but the efficacy of this dietary ketogenic treatment for intractable epilepsy is greater in younger infants suggesting a possible link the well-established but often overlooked importance of ketones in infant brain development.

During lactation, the human infant brain metabolises > 50% of the fuel provided, despite the brain representing only 12–13% of body's weight (Cunnane and Crawford, 2014). Glucose supplies about 30% of the late term fetus's brain energy requirements (Adam *et al.*, 1975) and about 50% of the neonate's brain energy requirements (Bougneres *et al.*, 1986); the difference is provided by ketones. Therefore, ketones are an obligate brain fuel during an infant's development, as opposed to being an alternative brain fuel in the adult human, *i.e.* only needed when glucose is limiting. Ketones are more than just catabolic substrates (fuel) for the developing brain – they are also important anabolic substrates because they supply the majority of carbon used to synthesize brain lipids such as cholesterol and long chain saturated and monounsaturated fatty acids (Cunnane *et al.*, 2003; Edmond, 1974; Yeh *et al.*, 1977).

7 Medium chain fatty acids as a source of ketones

Ketones are produced by *β*-oxidation of fatty acids. *β*-oxidation is mainly hepatic but may also occur in the gut and brain, especially during early development (Robinson and Williamson, 1980). The substrate fatty acids for ketogenesis may be short-, medium- or long-chain fatty acids (Bach *et al.*, 1996) and may originate from the diet or from fat stores in adipose tissue. In adults, long chain fatty acids stored in fat or consumed as dietary triglycerides are the primary source of carbon for ketogenesis, but in the breast-fed infant, MCFA in milk are the most important source of carbon for ketogenesis (Sarda *et al.*, 1987). MCFA from breast milk can be stored in infant fat so once breast-feeding has terminated, stored MCFA can still be liberated to provide ketones (Cunnane and Crawford, 2014). Coconut and palm oil are unusual amongst common dietary oils in that they contain some MCFA (mostly lauric acid [12:0] but also some caprylic [8:0] and capric [10:0] acids), so these oils are a simple, economical and well-accepted way to consume MCFA.

MCFA are more rapidly absorbed from the gut directly to the liver via the portal vein compared to long chain fatty acids which are absorbed primarily via the lymphatic duct and into the peripheral circulation (Fig. 2; Bach *et al.*, 1996). MCFA are also more easily *β*-oxidized in mitochondria because they do not require activation to CoA esters by carnitine (Fig. 3; Bach *et al.*, 1996). Both the rapid absorption and *β*-oxidation of MCFA suggest these fatty acids have a physiologically important function. Theoretically, this function could include elongation to long-chain fatty acids but, in practice, is probably limited to ketogenesis, especially in infancy which is the only period when it is normal to be regularly consuming MCFA.

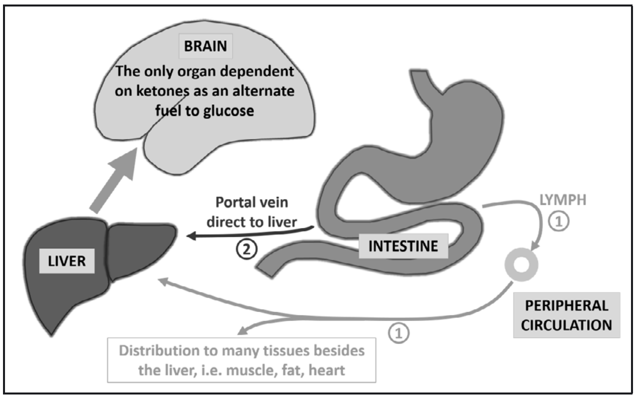

Fig. 2. Unique route of medium chain fatty acid (MCFA) absorption compared to other common long chain dietary fatty acids. The lymphatic and peripheral circulation ① distribute most common long chain fatty acids as chylomicrons throughout the body, whereas MCFA are mostly absorbed directly *via* the portal vein to the liver ②.

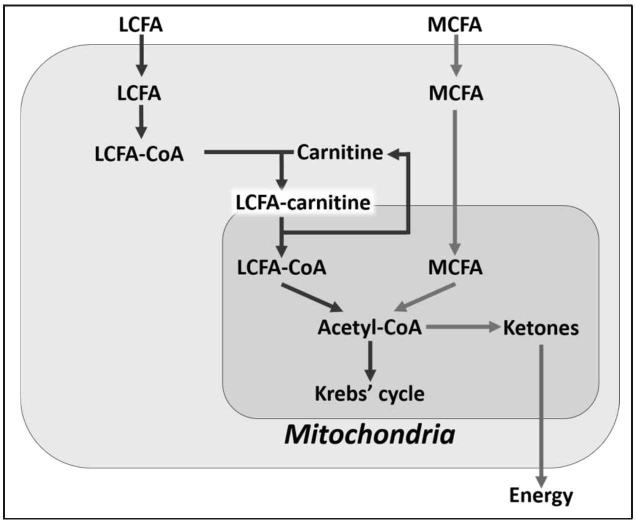

Fig. 3. Simpler beta-oxidation of medium chain fatty acids (MCFA) which, unlike long chain fatty acids (LCFA), do not need to be activated by carnitine to access the inner mitochondrial membrane. Very little acetyl-CoA enters the Krebs' cycle in the liver since the intermediates, oxaloacetate and malate, are consumed for glucose production. The high amount of NADH also allosterically inhibits the Krebs' cycle. These mechanisms result in the accumulation of acetyl-CoA in the liver and their subsequent condensation to ketones through a series of enzyme-catalyzed steps.

Long chain fatty acids are the main alternate fuel to glucose for most tissues. They can also be taken up by the brain but the reason they are not a useful fuel for the brain is because their rate of uptake is insufficient to meet the demand for energy once glucose becomes limiting. However, MCFA such as octanoate (caprylic acid) can be taken up rapidly and be metabolized by the brain (Auestad *et al.*, 1991; Ebert *et al.*, 2003; Eberts, 1961; Edmond, 1974; Kuge *et al.*, 1995; Robinson and Williamson, 1980). Whether MCFA have direct effects on the brain or are principally metabolized to ketones before exerting any effect as fuels, lipid substrates or lipid signalling molecules remains to be seen.

Table 1. Key points linking medium chain fatty acids, ketones and normal infant brain development.

Ketones supply > 30% of late brain and about 50% of neonatal brain energy needs	(Adam *et al.*, 1975) (Bougneres *et al.*, 1986)
Medium chain fatty acids are present at 10–15% of maternal milk fatty acids and 8–10% of neonatal body fat	(Sarda *et al.*, 1987)
Ketones supply ⩽90% of the carbon to make brain cholesterol, saturated fats	(Cunnane *et al.*, 2003)
Octanoic acid is rapidly taken up and metabolized by the brain	(Kuge *et al.*, 1995), (Ebert *et al.*, 2003)

8 Conclusion

Given the essential role of ketones in meeting the high energy requirements of the infant brain, it seems clear that ketogenesis from MCFA can serve as a physiological model for attempting to bypass problems of inadequate glucose uptake or metabolism in the adult brain. MCFA in the form of dietary medium chain triglycerides have a long history in clinical nutrition and are widely regarded as safe by government regulatory agencies. MCFA consist of several even- and odd-chain fatty acids from 6–12 carbons and it remains to be seen whether individual MCFA have distinctive metabolic or neurotherapeutic effects.

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