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Brain glucose and acetoacetate metabolism: a comparison of young and older adults

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ABSTRACT

The extent to which the age-related decline in regional brain glucose uptake also applies to other important brain fuels is presently unknown. Ketones are the brain's major alternative fuel to glucose, so we developed a dual tracer positron emission tomography protocol to quantify and compare regional cerebral metabolic rates for glucose and the ketone, acetoacetate. Twenty healthy young adults (mean age, 26 years) and 24 healthy older adults (mean age, 74 years) were studied. In comparison with younger adults, older adults had 8 ± 6% (mean ± SD) lower cerebral metabolic rates for glucose in gray matter as a whole ($p = 0.035$), specifically in several frontal, temporal, and subcortical regions, as well as in the cingulate and insula ($p \leq 0.01$, false discovery rate correction). The effect of age on cerebral metabolic rates for acetoacetate in gray matter did not reach significance ($p = 0.11$). Rate constants (min $^{-1}$) of glucose (Kg) and acetoacetate (Ka) were significantly lower (−11 ± 6%; [$p = 0.005$], and −19 ± 5%; [$p = 0.006$], respectively) in older adults compared with younger adults. There were differential effects of age on Kg and Ka as seen by significant interaction effects in the caudate ($p = 0.030$) and post-central gyrus ($p = 0.023$). The acetoacetate index, which expresses the scaled residuals of the voxel-wise linear regression of glucose on ketone uptake, identifies regions taking up higher or lower amounts of acetoacetate relative to glucose. The acetoacetate index was higher in the caudate of young adults when compared with older adults ($p \leq 0.05$ false discovery rate correction). This study provides new information about glucose and ketone metabolism in the human brain and a comparison of the extent to which their regional use changes during normal aging.

1. Introduction

In cognitively normal older adults, glucose uptake measured by positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has been reported to be lower in several brain regions relative to young adults, particularly in the precuneus, posterior cingulate, and parietal, temporal and frontal cortex (De Santi et al., 1995; Marano et al., 2012; Willis et al., 2002; Yanase et al., 2005). However, after correction for partial volume effects (PVE) mainly because of regional brain atrophy with age, either FDG uptake is no longer significantly different (Curiati et al., 2011; Ibanez et al., 2004; Yanase et al., 2005), or the only region in which FDG uptake remains significantly lower is in the frontal cortex (Kalpouzos et al., 2009). Lower regional glucose uptake is more pronounced in Alzheimer's disease, and may be of some use in the differential diagnosis of specific forms of aging-associated cognitive impairment (Chetelat et al., 2013; Kantarci et al., 2010; Li et al., 2008; Mosconi et al., 2009; Scheef et al., 2012). Lower regional brain glucose uptake is also present in young adults with a maternal family history of Alzheimer's disease (Mosconi et al., 2007) or with a genetic predisposition to Alzheimer's disease by

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virtue of carrying the apolipoprotein E ε4 allele (Reiman et al., 2004, 2005).

Glucose is the brain's predominant fuel under normal conditions but it is not the brain's only fuel (Cunnane et al., 2011; Gottstein et al., 1971; Owen et al., 1967). The ketones, acetoacetate [AcAc], and β-hydroxybutyrate are the brain's main alternative fuels to glucose in adult humans and are essential brain fuels during infant development (Cremer, 1982; Nehlig, 2004; Robinson and Williamson, 1980). In adult humans, plasma ketones commonly reach 2–3 mM during 3–6 days fasting, prolonged exercise, or on a very high fat ketogenic diet (Balasse and Fery, 1989; Cahill, 2006; Mitchell et al., 1995; Owen et al., 1967). The ketogenic response to fasting is essential to preserve muscle protein, which would otherwise be depleted to produce glucose for the brain from amino acids via gluconeogenesis (Veech et al., 2001). Indeed, during starvation, ketones can provide up to 70% of the brain's fuel requirements (Cahill, 2006; Hasselbalch et al., 1995; Owen et al., 1967; Robinson and Williamson, 1980). Normal brain function can be maintained by ketone infusion during acute, controlled experimental plasma glucose depletion (Amiel et al., 1991; Page and Williamson, 1971; Veneman et al., 1994).

Ketones use a different transport system to enter the brain (monocarboxylic acid transporters) than glucose (Morris, 2005; Pierre and Pellerin, 2005), and are catabolized to acetyl CoA independently of glycolysis (Mamelak, 2012; Veech et al., 2001). Unlike glucose, ketones are taken up and metabolized by the brain in direct proportion to their arterial concentration (Blomqvist et al., 2002; Cunnane et al., 2011; Hasselbalch et al., 1996). Glucose metabolism is largely separate from ketone metabolism but some carbon from glucose can be incorporated into ketones via acetyl CoA (Laffel, 1999). However, conditions that increase plasma glucose generally also increase plasma insulin which is the main inhibitor of ketone synthesis, thereby usually insuring that acetyl CoA from glucose goes either to the Krebs' cycle or to amino acid synthesis but not to ketogenesis.

Without measuring uptake of at least one other fuel that is taken up by the brain independently of glucose, it remains unclear as to whether lower brain glucose uptake in healthy older adults or in those at risk of Alzheimer's disease can be interpreted as being a generalized marker of deteriorating brain energy metabolism or could possibly be specific to glucose. Some brain regions taking up less glucose in older adults might still be functional but cannot obtain or metabolize enough glucose because of a problem related to glucose transport or usage (Cunnane et al., 2011; Maalouf et al., 2009; Mamelak, 2012; Swerdlow, 2009). If that were the case, a fuel accessing the tricarboxylic acid cycle independently of glycolysis, that is ketones, would not necessarily display the same pattern of brain hypometabolism as glucose. Equally importantly, brain regions that apparently take up glucose normally during aging may not necessarily be able to adequately take up ketones, yet both are important for optimal brain function.

We therefore developed carbon-11 acetoacetate (^{11}C-AcAc) as a PET ketone tracer (Tremblay et al., 2007) to use in parallel with FDG in studying brain energy metabolism during aging. Our objective was to assess the extent to which the regional pattern of brain ^{11}C-AcAc uptake resembles that of FDG in healthy, cognitively normal young and older adults. We established a brain PET protocol in which ^{11}C-AcAc is the first tracer injected because of its shorter half-life of ^{11}C (20 minutes), followed by a wash-out period and then injection of FDG. PET images were co-registered to each participant's respective magnetic resonance (MR) images, and brain regions were segmented for quantitative PET tracer uptake analysis after PVE correction (Quarantelli et al., 2004).

The tracer uptake data was expressed in 3 ways: (1) cerebral metabolic rate (μmol/100 g/min) of glucose (CMRg), and AcAc (CMRa); (2) rate constants (min^{-1}) of glucose (Kg) and AcAc (Ka), and; (3) the acetoacetate index (AI). CMR is the traditional measure for quantifying brain fuel uptake and is the product of K multiplied by the plasma concentration of the metabolite in question. Plasma ketones vary markedly even under well-controlled conditions and so directly influence CMRa variability, thereby potentially masking differences with age (Lying-Tunell et al., 1981). Reporting the Ka considerably reduces this variability and potentially reveals differences in brain AcAc uptake not otherwise detectable. The AI is based on the approach of Vaishnavi et al. (2010) in which the scaled residuals of the voxel-wise linear regression of glucose on ketone uptake identify regions of the brain taking up higher or lower amounts of ^{11}C-AcAc relative to FDG.

2. Methods

2.1. Participants

Ethical approval for this study was obtained from the Research Ethics Committee of the Health and Social Services Center–University of Sherbrooke Geriatrics Institute, which oversees all human research at the Research Center on Aging. All participants provided written informed consent before study entry. Participants were between either 18–30 years old (young group; n = 20), or 65–85 years old (older adult group; n = 24). They all underwent a pre-screening visit, which included blood analysis based on a blood sample collected after an overnight fast, and completion of a medical history questionnaire. Exclusion criteria included a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score <26/30, smoking, diabetes, or glucose intolerance (elevated fasting plasma glucose, insulin or glycated hemoglobin), evidence of overt heart, liver or renal disease, and untreated hypertension, dyslipidemia, or thyroid disease. None of the young participants were medicated. Ten of the 24 older adult participants were medicated, 7 for hypertension (irbesartan, ramipril, or telmisartan), 2 for osteoporosis (risedronate), and 2 with a gastric acid secretion inhibitor (pantoprazole).

2.2. Magnetic resonance imaging

For each participant, three-dimensional T_1-weighted MR images were acquired on a 1.5 Tesla scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). The parameters of the gradient echo sequence were: repetition time/echo time - 16.00/4.68 ms, 20° flip angle, 1 mm^3 isotropic reconstructed voxel size, 256 × 240 × 192 mm^3 field of view, matrix size of 256 × 256 × 164, number of averages of 1, and an acquisition time of 9.14 minutes. A set of 20 fluid attenuated inversion recovery images were also acquired in the axial direction. The parameters were: repetition time/echo time - 8500/91 ms, 2400 ms inversion time, echo train length of 17, matrix size of 256 × 192, for a 230 × 172.5 mm^2 field of view, slice thickness of 6 mm, spacing between slices of 1.2 mm, number of acquisitions of 1, and an acquisition time of 3.09 minutes. Fluid attenuated inversion recovery MR images of the brain were reviewed by a neurologist and no evidence of structural abnormality was found in any young or older adult participant.

2.3. PET and cerebral metabolic rates

^{11}C-AcAc was synthesized as described previously (Tremblay et al., 2007). Brain PET scans were performed on a Philips Gemini TF PET/CT scanner (Philips Medical System, Eindhoven, The Netherlands) using a dynamic list mode acquisition, with time-of-flight enabled, an isotropic voxel size of 2 mm^3, field-of-view of 25 cm, and an axial field of 18 cm. For ^{11}C-AcAc, the time frames