Experimental Gerontology 107 (2018) 18–26

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease

E. Croteau [a,b], C.A. Castellano [a], M. Fortier [a], C. Bocti [a,c], T. Fulop [a,c], N. Paquet [d,e], S.C. Cunnane [a,b,c,*]

[a] Research Center on Aging, Université de Sherbrooke, Sherbrooke, Canada
[b] Department of Pharmacology & Physiology, Université de Sherbrooke, Sherbrooke, Canada
[c] Department of Medicine, Université de Sherbrooke, Sherbrooke, Canada
[d] Departments of Nuclear Medicine, Université de Sherbrooke, Sherbrooke, Canada
[e] CHUS Research Center, Université de Sherbrooke, Sherbrooke, Canada

ARTICLE INFO

Article history:
Received 14 March 2017
Received in revised form 30 June 2017
Accepted 1 July 2017
Available online 12 July 2017

Keywords:
Brain metabolism
Ketones
Acetoacetate
Glucose
Mild cognitive impairment (MCI)
Alzheimer's disease (AD)

ABSTRACT

Introduction: Deteriorating brain glucose metabolism precedes the clinical onset of Alzheimer's disease (AD) and appears to contribute to its etiology. Ketone bodies, mainly β-hydroxybutyrate and acetoacetate, are the primary alternative brain fuel to glucose. Some reports suggest that brain ketone metabolism is unchanged in AD but, to our knowledge, no such data are available for MCI.
Objective: To compare brain energy metabolism (glucose and acetoacetate) and some brain morphological characteristics in cognitively healthy older adult controls (CTL), mild cognitive impairment (MCI) and early AD.
Methods: 24 CTL, 20 MCI and 19 AD of similar age and metabolic phenotype underwent a dual-tracer PET and MRI protocol. The uptake rate constants and cerebral metabolic rate of glucose (K_{Glu}, CMR_{Glu}) and acetoacetate (K_{AcAc}, CMR_{AcAc}) were evaluated with PET using [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG), a glucose analogue, and [^{11}C]-acetoacetate ([^{11}C]-AcAc), a ketone PET tracer. Regional brain volume and cortical thickness were evaluated by T1-weighted MRI.
Results: In AD compared to CTL, CMR_{Glu} was ~11% lower in the frontal, parietal, temporal lobes and in the cingulate gyrus ($p < 0.05$). K_{Glu} was ~15% lower in these same regions and also in subcortical regions. In MCI compared to CTL, ~7% glucose hypometabolism was present in the cingulate gyrus. Neither regional nor whole brain CMR_{AcAc} or K_{AcAc} were significantly different between CTL and MCI or AD. Reduced gray matter volume and cortical thinning were widespread in AD compared to CTL, whereas, in MCI compared to CTL, volumes were reduced only in the temporal cortex and cortical thinning was most apparent in temporal and cingulate regions.
Discussion: This quantitative kinetic PET and MRI imaging protocol for brain glucose and acetoacetate metabolism confirms that the brain undergoes structural atrophy and lower brain energy metabolism in MCI and AD and demonstrates that the deterioration in brain energy metabolism is specific to glucose. These results suggest that a ketogenic intervention to increase energy availability for the brain is warranted in an attempt to delay further cognitive decline by compensating for the brain glucose deficit in MCI and AD.

1. Introduction

Regional brain glucose hypometabolism is one of the hallmarks of Alzheimer's disease (AD) (Brown et al., 2014). [^{18}F]-Fluorodeoxyglucose (FDG), a glucose analogue and radiotracer for positron emission tomography (PET) studies, has been extensively studied to assess the magnitude and progression of impaired brain glucose uptake in AD (Brown et al., 2014; Cunnane et al., 2016a). Like other groups, we have used PET-[^{18}F]-FDG and reported the now classical regional brain glucose hypometabolism pattern in mild AD (Castellano et al., 2015; Castellano et al., 2017; Cunnane et al., 2016a; Dukart et al., 2013; Mosconi et al., 2009).

Ketones (β-hydroxybutyrate and acetoacetate), are the brain's primary alternative fuel when plasma glucose is decreased. In prolonged starvation, ketones can supply up to 80% of adult human brain energy requirements (Cahill, 2006). Brain ketone utilization is directly proportional to blood ketone level over a wide blood ketone concentration range (Courchesne-Loyer et al., 2016; Nugent et al., 2014). Using the PET ketone tracer, ^{11}C-acetoacetate (AcAc), we have reported that

* Corresponding author at: Research Center on Aging, 1036 Belvedere St South, Sherbrooke, Quebec, J1H 4C4. Canada
E-mail address: stephen.cunnane@usherbrooke.ca (S.C. Cunnane).

http://dx.doi.org/10.1016/j.exger.2017.07.004
0531-5565/

Table 1
Characteristics of the cognitively healthy older controls (CTL) and patients with mild cognitive impairment (MCI) or early Alzheimer disease (AD).

	CTL ($n = 24$)	MCI ($n = 20$)	AD ($n = 19$)
Age (y)	72.8 ± 5.8	76.9 ± 5.8	73.1 ± 4.8
Gender (M/F)	10/15	9/12	8/11
Mini-mental state examination (score/30)	29.4 ± 0.9	27.5 ± 2.0*	25.5 ± 2.4*
Body mass index	26.7 ± 3.8	26.5 ± 3.1	24.3 ± 2.9
Glucose (mM)	5.2 ± 0.5	5. ± 0.4	5.4 ± 0.6
Hemoglobin A1c (%)	5.8 ± 0.3	5.6 ± 0.5	5.9 ± 0.4
Acetoacetate (mM)	0.12 ± 0.08	0.14 ± 0.05	0.11 ± 0.07
β-hydroxybutyrate (mM)	0.25 ± 0.18	0.25 ± 0.12	0.21 ± 0.16

* One-way ANOVA and Tukey's post hoc test $p < 0.05$.

brain metabolism of ketones is unchanged in early AD (Castellano et al., 2015; Castellano et al., 2017; Cunnane et al., 2016a). Our results confirm earlier reports that used the arterio-venous difference method and showed that brain ketone uptake is still normal in moderately advanced AD (Lying-Tunell et al., 1981; Ogawa et al., 1996).

Mild cognitive impairment (MCI) is the prodromal state to AD (Gauthier et al., 2006). Objective evidence of cognitive decline is present in MCI but it does not yet interfere with the activities of daily living. Impaired glucose metabolism is also present in certain brain regions in MCI (Jicha et al., 2008; Pagani et al., 2015) but whether brain ketone uptake is altered in MCI has not been reported.

The primary aim of the present study was to compare brain ketone and glucose consumption in a cross-sectional study of age-matched cognitively healthy older adults, MCI and AD. Our secondary aim was to assess the presence of brain atrophy and thinning of the brain cortex in these three groups.

2. Material and methods

2.1. Participants

This study was approved by the institutional review board and ethics committees (Health and Social Services Center, Sherbrooke University Geriatrics Institute and the Centre hospitalier universitaire de Sherbrooke) and written informed consent was obtained for all participants. Participants underwent a pre-screening visit including medical history questionnaire and blood analysis. Exclusion criteria included smoking, substance abuse, and untreated/uncontrolled hypertension, dyslipidemia or diabetes. Cognitively healthy older adults (CTL, $n = 24$) had a Mini-Mental State Examination (MMSE) score of ≥27/30. Criteria for inclusion in the MCI group ($n = 20$) were: subjective memory complaint, score below the normative normal score for age in one or more cognitive domains (typically including episodic memory, language and executive function), intact score of activities of daily living (score ≤ 15/24 at the IADL subscale of the Functional Autonomy Measuring System; (Hebert et al., 1988)), plus no evidence of AD or depression (score ≤ 10 on the Geriatric Depression Scale 30-items). (Petersen, 2004). Probable or possible AD ($n = 19$) was defined using the National Institute on Aging - Alzheimer's Association (NIA-AA) criteria (Castellano et al., 2017; McKhann et al., 2011) with or without use of prescribed medication for AD.

2.2. PET and MRI neuroimaging protocols

After a light breakfast, participants fasted for about 6 h before starting the imaging session. All participants underwent a 3D T1-weighted MRI at 1.5 or 3 T (Pfefferbaum et al., 2012). The protocol for the 1.5 T MRI scans (Sonata, Siemens Medical Solutions, Erlangen, Germany) was as follows:

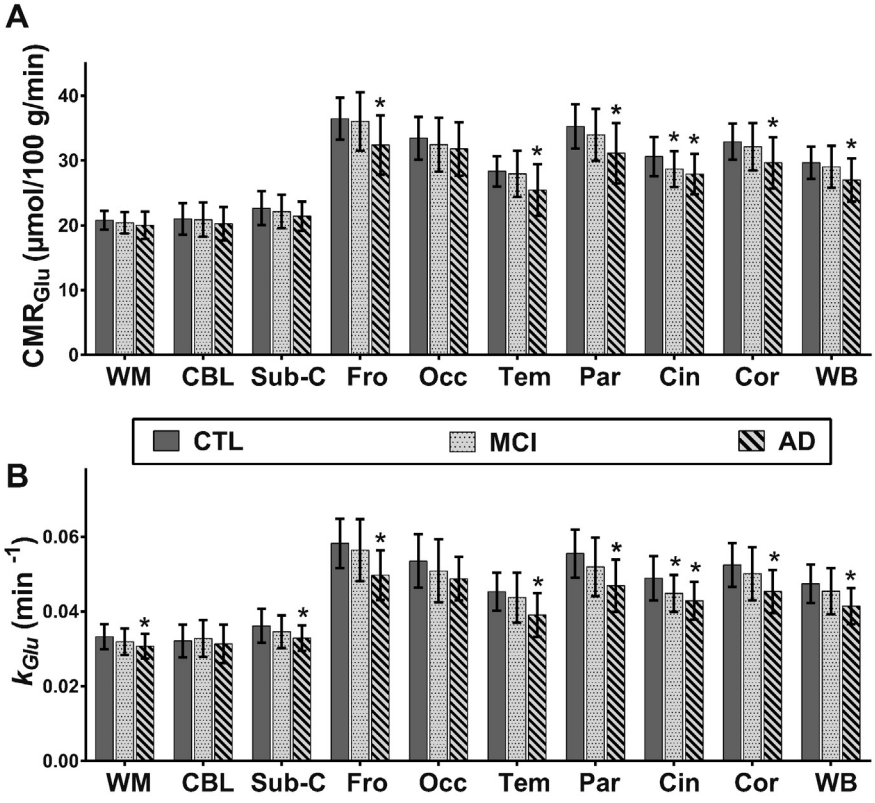

Fig. 1. Regional and whole brain glucose (^{18}F–flurodeoxyglucose) uptake in healthy older controls (CTL; $n = 24$), mild cognitive impairment (MCI; $n = 20$) and early Alzheimer's disease (AD; $n = 19$). **A**: Regional cerebral metabolic rate of glucose per unit of brain tissue (CMR_{Glu}). **B**: Regional constant rate uptake (K_{Glu}). WM; white-matter, CBL; cerebellum, Sub-C; subcortical region (thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens), Fro; frontal, Occ; occipital, Tem; temporal, Par; parietal, Cin; cingulate, Cor; cortex, WB; whole brain. Data are presented as mean ± SD; * $p < 0.05$, one way ANOVA with post-hoc Tukey tests.