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Brain fuel uptake during aging and in Alzheimer's disease: A positron emission tomography and MRI study comparing glucose and a new ketone tracer – ^{11}C -acetoacetate

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Lower regional cerebral metabolic rate of glucose (CMR_g) is present during normal aging and may contribute to the development or progression of Alzheimer's disease (AD)⁽¹⁾. However, with only [^{18}F]-fluorodeoxyglucose (^{18}F -FDG) available to measure brain energy metabolism by positron emission tomography (PET), it remains unclear whether lower CMR_g in AD represents a global problem of brain energy substrate metabolism or is specific to glucose. The ketones, acetoacetate (AcAc) and beta-hydroxybutyrate, are the brain's main alternative energy substrates to glucose during prolonged fasting or in other forms of glucose deficit, so we compared brain glucose and AcAc metabolism in three groups: young healthy adults, healthy elderly and mild AD. Our objectives were to: (i) quantify CMR_g and brain [^{11}C]-AcAc uptake (CMR_a) by PET, and (ii) compare regional brain volumes, CMR_g and CMR_a between healthy young and elderly persons, and between the healthy elderly and mild AD.

Twelve young adults (30 y old), fifteen healthy elderly (76 y old) and eight mild AD (77 y old) were evaluated. Diagnostic of mild AD was established according to recognised criteria. Volumetric MRIs were acquired on a Siemens 1.5T scanner. PET images were acquired on a Philips Gemini TF scanner. Freesurfer and PMOD[®] 3.3 software were used to calculate regional brain volumes and quantify and CMR_g and CMR_a ($\mu\text{mol}/100\text{g}/\text{min}$). Data were compared using a *t*-test (healthy young vs. elderly and healthy elderly vs. mild AD). A 0.01 FDR correction was applied to correct for multiple comparisons.

Mini-Mental State Examination scores ($/30$; mean [SD]) did not differ significantly between the healthy young 29.6 [0.7] and elderly 29.1 [1.0]. Compared to the young adults, the elderly had lower volume of total gray matter (-16%; $p < 0.001$), thalamus (-16%; $p < 0.001$), and hippocampus (-12%; $p < 0.004$), and 133% higher ventricular volume ($p < 0.001$). Mild AD was associated with 18% lower intracranial volume, 12% lower white matter volume, and 68% larger ventricles compared to the healthy elderly ($p < 0.001$). Hippocampal volume was 22% lower in mild AD ($p < 0.003$). Global CMR_g was 7% lower in the elderly ($p < 0.006$), a difference present in 8/64 brain regions studied, mostly in the frontal cortex, thalamus and caudate. Global CMR_a was 17% lower in the elderly ($p < 0.007$), a deficit present mostly in the frontal cortex and cingulate. Global CMR_g was 21% lower in AD compared to the elderly ($p < 0.006$), a deficit present in six brain regions mostly in the cingulate, parietal cortex, precuneus and thalamus. CMR_a was 46% lower in AD compared to the elderly ($p < 0.003$), a deficit present specifically in the amygdala and caudate.

We conclude that regional brain fuel uptake is lower in the healthy elderly and in mild AD, and affects both brain glucose and ketone (AcAc) metabolism. Specific regions with lower brain fuel uptake were different in the healthy elderly from those with mild AD. In both the elderly and in mild AD, the brain regions in which glucose uptake was lower were also different from those with lower AcAc uptake, suggesting for the first time that regional brain hypometabolism in the elderly is fuel-specific.

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1. Cunnane S, Nugent S, Roy M *et al.* (2011) *Nutrition* 27: 3–20.