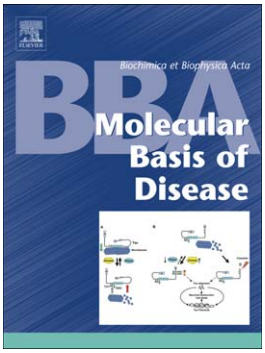

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Graded Perturbations of Metabolism in Multiple Regions of Human Brain in Alzheimer's Disease: Snapshot of a Pervasive Metabolic Disorder

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Running title: Altered metabolite patterns in human AD-brain

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disorder that displays pathological characteristics including senile plaques and neurofibrillary tangles. Metabolic defects are also present in AD-brain: for example, signs of deficient cerebral glucose uptake may occur decades before onset of cognitive dysfunction and tissue damage. There have been few systematic studies of the metabolite content of AD human brain, possibly due to scarcity of high-quality brain tissue and/or lack of reliable experimental methodologies. Here we sought to: 1) elucidate the molecular basis of metabolic defects in human AD-brain; and 2) identify endogenous metabolites that might guide new approaches for therapeutic intervention, diagnosis or monitoring of AD. Brains were obtained from nine cases with confirmed clinical/neuropathological AD and nine controls matched for age, sex and *post-mortem* delay. Metabolite levels were measured in *post-mortem* tissue from seven regions: three that undergo severe neuronal damage (hippocampus, entorhinal cortex and middle-temporal gyrus); three less severely affected (cingulate gyrus, sensory cortex and motor cortex); and one (cerebellum) that is relatively spared. We report a total of 55 metabolites that were altered in at least one AD-brain region, with different regions showing alterations in between 16 and 33 metabolites. Overall, we detected prominent global alterations in metabolites from several pathways involved in glucose clearance/utilization, the urea cycle, and amino-acid metabolism. The finding that potentially toxigenic molecular perturbations are widespread throughout all brain regions including the cerebellum is consistent with a global brain disease process rather than a localized effect of AD on regional brain metabolism.