Transcriptome-To-Metabolome™ Biosimulation Reveals Human Hippocampal Hypometabolism with Age and Alzheimer’s Disease

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ABSTRACT

The authors had validated a proprietary method, Transcriptome-To-Metabolome™ (TTM™) Biosimulation, for using the transcriptome to determine parameters for kinetic biosimulation of 16 core metabolic pathways. In vivo and in silico evidence confirmed that hippocampal cholesterol metabolism decreases with aging and increases with Alzheimer’s disease (AD). The molecular studies on aging primate and human hippocampus, including AD samples, provided internal validations on the biosimulations, while evidence from the literature, bibliome, provided external validations. This study extends the investigations with the TTM™ Biosimulations into the changes in these 16 metabolic pathways in aging male human hippocampus and for stages of AD. The authors report robust hippocampal hypometabolism in the fifth to tenth decade of life involving glucose and lipid metabolism in male humans. These findings are validated externally from the bibliome. Several changes in AD are demonstrated to be exaggerations or deviations of very late stage changes of normal aging among these pathways.

Keywords: Aging, Brain, Computational Biology, Genome Wide Microarray Analysis, Metabolome, Neurodegeneration, Predictive Simulation

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INTRODUCTION

Humans intuitively know that metabolism decreases with age, either by observing the elderly or by aging themselves. This accepted fact is not always revealed in contemporary studies using state-of-the-art brain imaging techniques (Curiaji et al., 2011), reaffirming the conclusions by Kety (1956) that decrements in observed metabolic activity of the aging brain are due to loss of tissue volume. This evidence calls to question recent reports on hypometabolism in the hippocampus with normal aging, thereby, confusing interpretations of additional changes with Alzheimer’s disease (AD) (Mosconi et al., 2008; Reiman et al., 2010; Sheng et al., in press). On the other hand, several contemporary studies have given strong indications for loss of metabolic capacity in remaining brain tissue with age according to genomics (De Jager et al., in press), transcriptomics (Berchtold et al., 2008; Blalock et al., 2010; Rowe et al., 2007), proteomics (Freeman et al., 2009; Yang et al., 2008), metabolomics (Salek et al., 2008; Zhang et al., 2009), and lipidomics (Rapley et al., 2009). The Transcriptome-To-Metabolome™ (TTM™) Biosimulation method used in this study demonstrates that there is indeed a robust decrement in several metabolic pathways in the aging human male hippocampus. Once establishing this normal age-related change, the status of metabolism in the hippocampus for severe AD is assessed with the same TTM™ method, supporting the assertion that homeostasis has shifted as an attempt for protection (Sun et al., 2011) possibly associated with age-related myelin breakdown (Bartzokis, 2011).

The history of demonstrating this decrement of metabolism, i.e., hypometabolism, from early to later life, or pubescence to senescence, is well established. Reiner (1947) showed that respiration in rat brain dropped rapidly after 24 months of age, and was constant through adulthood, a level that was greater than seen at birth. In that era and today, tissue homogenates and subcellular fractions were assayed for enzyme activities ex vivo revealing increases for some enzymes and decreases for others (Iwangoff et al., 1980; El-Hassan et al., 1981; Gaiti et al., 1981; Baquer et al., 1990; Kish et al., 1998). Kety (1955) used cerebral blood flow and oxygen consumption, as well as ‘mined data’ on cortical neuronal density, to demonstrate a rapid decrease in all three parameters in humans from age 5 to 93 years. The next technical era, from 1950s to 2010 even, utilized in situ histochemistry for enzyme activity (Kaneta, 1966; Wilson, 1983) and hybridization for mRNA levels (Cimino et al., 1994) alone or combined with ex vivo enzyme assays and protein quantitation with Western blot (Bigl et al., 2003; Yao et al., 2010). Collectively with the ‘omics evidence mentioned above, we hypothesized that utilization of gene expression levels (of the hippocampal tissue still persisting at ever advancing ages in humans) to determine the kinetic parameters of TTM™ Biosimulations on the core metabolic pathways would reveal whether metabolism decreases with normal aging.

Our prior work had demonstrated many changes with normal aging and in AD hippocampus (Phelix et al., 2011). With further investigation on the pathways affected, our method disclosed several new details about the link between the hypometabolism and more distantly related effects on potentially damaging alterations to neurochemistry. Most remarkable is the accumulation of dihydroxyacetone phosphate (DHAP) in aging hippocampus that can oxidize spontaneously to methylglyoxal and form protein adducts as advanced glycation end products (Di Loreto et al., 2004; Orosz et al., 2009). The level of these hippocampal adducts can be used to predict the age of the human, postmortem (Sato et al., 2001). Our results provide explanations on how DHAP increases in aging brain tissue and becomes available to cause many far reaching detrimental effects (Hipkiss, 2010). The biggest lesson is that one must know which earlier age is the reference for older age associated changes and, whether the comparison by decade or larger age groups.
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