GSK3β Regulates Brain Energy Metabolism

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Abstract
Age is the greatest risk factor for Alzheimer’s disease (AD) and countless studies have linked growth and energy metabolism to age-related disease vulnerability. Indeed, the growth signaling network, glycogen synthase kinase-3 (GSK3β) has been directly linked to the principle biochemical hallmarks of AD, tau tangles and beta-amyloid plaques. We previously identified a novel metabolic pathway whereby GSK3β regulates the stability and activity of peroxisome proliferator-activated receptor gamma coactivator 1-sigmas (PGC-1s), a master regulator of mitochondrial function (Anderson et al. 2008). Here, we characterize the extent to which GSK3β regulates metabolism at the cellular level using lithium, a widely-used inhibitor of GSK3β. Lithium treatment resulted in upregulation of mitochondrial metabolism in cell culture models of astrocytes and mature neurons. This shift in metabolism involved increases in basal and maximal oxygen consumption, mitochondrial potential, and lengthening of NAD(P)H fluorescence lifetime in H4 cells, suggesting higher levels of protein bound NAD(P)H. Co-incident with these changes was an increase in the stability of PGC-1α protein, which rapidly localized to the nucleus upon lithium administration. Overexpression of GSK3β in cells revealed a significant role for GSK3β in the regulation of myriad metabolic processes, such as NAD(P)H turnover, with age could contribute to disease vulnerability. Finally, mice fed a diet of lithium can better withstand the month-long lengthening of NAD(P)H fluorescence lifetime in key areas of the hippocampus and alteration in cytochrome c oxidase activity in a highly region and cell-type specific manner, suggesting that GSK3β operates similarly in regulating metabolism of the whole-brain. Altogether, these results suggest a role for GSK3β as a driver of metabolic dysfunction with age. It also appears that metabolism itself, and the GSK3β as a driver of metabolic dysfunction with age.

Background
Cells Realizing (CR) is a well-established model of delayed aging that prolongs lifespan and reduces the cumulative effects of aging. In the current project, we explore the extent to which GSK3β contributes to energy metabolism, a function that is highly responsive to CR.

Conclusions:
GSK3β regulates multiple facets of cellular energy metabolism:
- Basal and maximal respiration
- Mitochondrial membrane potential
- Redox function
- NAD(P)H metabolism

Importantly, these effects appear to be conserved from the level of individual cells to the whole brain, where the impact of GSK3β inhibition is highly cell-type and region specific.

We propose a model of the aging brain in which GSK3β drives multiple, convergent aspects of neurodegeneration, particularly energy metabolism.