Long Term Intranasal Insulin to Combat Cognitive Decline

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The hippocampus plays a critical role in learning and memory and is impacted significantly early during the aging process. Together with an increase in the aging population, and an elevation in the prevalence of neurodegenerative diseases with aging, it is clear that more efforts have to be dedicated to the pursuit of novel therapeutics for the treatment of age-associated cognitive decline. Recent studies have suggested that insulin resistance may play a role in the manifestation of cognitive decline seen in aging and Alzheimer's disease (AD). The role or presence of central insulin resistance in the brain, however, has yet to be completely elucidated, and it is also not clear whether long-term exposure to insulin can cause similar decline in signaling in the brain as it does in the periphery. Previous studies from our lab have looked at relatively short-duration intranasal insulin administration in rat models (Humalog, Apidra, Levemir). Insulin analogs were used to characterize changes in peripheral blood glucose, and in learning and memory function in aged and young rodents across several doses (Anderson et al., 2016; Maimaiti et al., 2016). In this study, we looked at the effect of long-term intranasal Aspart insulin (daily for ~3 months) in young and aged male F344 rats. Behavior was characterized using the Morris water maze. Left brain hemispheres were post-fixed in paraformaldehyde and sectioned for immunohistochemistry with an anti-insulin receptor antibody. While a robust aging effect between groups was noted in saline treated animals, repeated treatment with intranasal insulin was unable to offset cognitive decline in aged animals. Of interest, we saw a significant aging and drug effect along with a significant interaction term on the insulin receptor immunochemistry of dorsal hippocampus sections. Early data analysis indicates that long-term intranasal insulin exposure affects insulin receptor immunolabeling differently between young and aged animals and could well lead to downregulation of receptors as it does in the periphery, albeit on a longer time scale.