Abstract:

Neuronal insulin signaling is crucial for regulating glucose metabolism, neuronal survival, and cognitive functions in the brain, with disruptions contributing to insulin resistance and potentially leading to Type 2 diabetes (T2D) and Alzheimer's disease (AD). Despite exercise's well-documented benefits for body and brain health, the specific brain signaling mechanisms remain unclear, and *in vitro* studies are limited. We investigated alternative pathways to maintain glucose homeostasis beyond traditional insulin signaling. Using an ATP-mediated neuronal *in vitro* exercise model, we observed elevated levels of markers upregulated by exercise, increased glucose uptake, and activation of insulin signaling molecules. Under insulin-resistance conditions, ATP surpassed insulin, acting as an exercise-like bypass mechanism. Similarly, Irisin, an exerkine released during exercise, has been implicated in muscle–brain communication and metabolic regulation. We examined its effects on hippocampal HT22 cells under both insulin-sensitive and insulin-resistant conditions. Acute Irisin treatment significantly upregulated exercise-related markers, and phosphorylated FAK, as part of its established integrin-FAK signaling axis. Additionally, Irisin also stimulated neuronal insulin signaling, promoting Akt, As160, GSK3 phosphorylation and GLUT4 translocation to enhance glucose uptake. However, under chronic hyperinsulinemia-induced insulin resistance, Irisin's effects were impaired. These findings suggest that while ATP can bypass insulin resistance, Irisin's neurotrophic and insulin signaling effects require intact insulin signaling. Together, our results suggest a possible role for ATP and Irisin in the context of T2D and AD.