The Role of NDRG1 in Neuronal Insulin Signaling

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ABSTRACT

Insulin signaling plays a central role in maintaining systemic metabolic homeostasis by regulating glucose uptake and nutrient utilization across multiple tissues. In recent years, insulin signaling within the central nervous system has emerged as an important regulator of neuronal metabolism, synaptic plasticity, cognition, and whole-body energy balance. Consequently, impaired neuronal insulin signaling has been strongly associated with metabolic disorders, cognitive dysfunction, and neurodegenerative diseases including Alzheimer's disease. Canonical insulin signaling primarily proceeds through the PI3K/Akt signaling pathway, culminating in phosphorylation of downstream substrates such as AS160 and subsequent glucose uptake. Although several kinases and phosphatases regulating this pathway have been identified, the molecular mechanisms governing neuronal insulin signaling and insulin resistance remain incompletely understood.

Members of the N-myc downstream regulated gene (NDRG) family have been implicated in several signaling pathways associated with proliferation, differentiation, cellular stress responses, and survival. Among these, NDRG1 has been reported to interact with signaling molecules including PTEN, GSK3β, PKCα, and PP2A, suggesting a potential role in insulin signaling regulation. Nevertheless, direct experimental studies investigating the role of NDRG1 in insulin signaling remained largely absent prior to the present work. Therefore, the present study investigated the role of NDRG1 in neuronal insulin signaling and insulin resistance, with particular emphasis on canonical Akt–AS160 signaling, neuronal glucose uptake, and PTEN regulation.

The findings of this study demonstrate, for the first time, that NDRG1 functions as a regulator of canonical neuronal insulin signaling and neuronal glucose uptake. Modulation of NDRG1 expression significantly altered insulin-stimulated Akt phosphorylation, AS160 phosphorylation, and glucose uptake in neuronal cells. Silencing of NDRG1 enhanced Akt and AS160 phosphorylation and increased neuronal glucose uptake, whereas overexpression of NDRG1 produced the opposite effect, indicating that NDRG1 negatively regulates canonical insulin signaling. Furthermore, phosphorylation of NDRG1 at Thr346 and integrity of its C-terminal region were found to be important for coordinated regulation of Akt signaling, AS160 phosphorylation, and glucose uptake, suggesting that NDRG1 functions as a phosphorylation-dependent signaling regulator.

The study further demonstrated that NDRG1 regulates PTEN C-terminal phosphorylation in the context of neuronal insulin signaling. Neuronal insulin resistance is associated with reduced phosphorylation of PTEN at Ser380/Thr382/Thr383, residues located within the inhibitory C-terminal tail of PTEN. Modulation of NDRG1 expression significantly altered phosphorylation of PTEN at these residues, while insulin-resistant conditions enhanced the interaction between NDRG1 and PTEN. Experimental observations additionally suggested involvement of protein phosphatase 2A (PP2A) in NDRG1-mediated regulation of PTEN phosphorylation. Collectively, these findings support a model in which NDRG1 participates in regulation of PTEN activity in neurons by modulating its phosphorylation at Ser380/Thr382/Thr383, in the context of insulin signalling and insulin-resistance.

Together, the findings of this thesis identify NDRG1 as a previously unrecognized phosphorylation-dependent regulator of neuronal insulin signaling. The present work expands current understanding of neuronal insulin resistance and provides a framework for future investigations examining the relationship between metabolic dysfunction, neuronal signaling, and neurodegenerative disease.