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SPOTLIGHT

Neuronal GDPGP1 and glycogen metabolism: friend or foe?

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The adult brain consumes glucose for energy needs and stores glucose as glycogen mainly in astrocytes. Schulz et al. (2020. *J. Cell Biol.* https://doi.org/10.1083/jcb.201807127) identify the stress-regulated metabolic enzyme GDPGP1 that promotes neuronal survival likely through glycogen reserves in mouse and *C. elegans* neurons.

To support its complex and dynamic activities, the human brain accounts for over 20% of the body's total energy consumption. Neurons account for most of this energy expenditure and rely primarily on oxidative phosphorylation. In fact, neurons are so sensitive to oxygen and glucose deprivation, that just a few minutes of hypoxia or hypoperfusion induces irreversible neuronal damage. As such, therapies aimed at improving neuronal metabolic resilience are of great clinical value in the treatment of stroke, neonatal hypoxic-ischemic encephalopathy, and neurodegenerative diseases. To that end, Schulz et al. sought to discover new stress-responsive and potentially cytoprotective neuronal genes using an innovative approach integrating experiments and analyses using mouse embryonic neuronal cultures and *Caenorhabditis elegans* (1). The authors uncovered an evolutionarily conserved maladaptive pathway that links metabolic stress to decreased neuronal GDPDP1/MCP-1 abundance and increased neuronal vulnerability. Their intriguing findings raise many questions concerning the normal physiological role of GDPGP1/MCP-1 and reignite an old debate concerning the neuroprotective versus neurotoxic roles of glycogen metabolic pathways and metabolism in neurons.

Schulz and colleagues used unbiased transcriptomic sequencing of primary mouse embryonic neurons exposed to two paradigms of cellular stress (oxygen-glucose deprivation and kainic acid exposure) to hone in on candidate cytoprotective transcripts (1). They narrowed their focus to the conserved metabolic enzyme GDPGP1/MCP-1 after finding its loss conferred the highest sensitivity to hypoxia in *C. elegans* out of all tested candidates. GDPGP1 catalyzes the conversion of GDP-D-glucose to glucose-1-phosphate (G1P), thus its inhibition results in reduced G1P and, indirectly, cellular glycogen levels. Furthermore, the authors found that even though GDPGP1/MCP-1 is cytoprotective, its gene expression is reduced by a variety of stresses in both *C. elegans* neurons and mouse embryonic neurons in vitro. Using gain- and loss-of-function genetic approaches, they show that high abundance of GDPGP1/MCP-1 protects against hypoxia stress and a *C. elegans* model of tauopathy, and that this protection is correlated with normal G1P and glycogen levels. These experiments indicate a key role for GDPGP1/MCP-1 in maintaining glycogen for neuronal stress resistance. Although additional experiments are required to fully elucidate the mechanistic details, the authors surmise that neuronal down-regulation of GDPGP1/MCP-1 and consequent loss of neuronal glycogen is a maladaptive response that limits neuronal stress resistance and reduces survival. This supports emerging, but still controversial lines of evidence linking normal neuronal functions and survival under stress to glycogen metabolism.

Conventional wisdom states that although neurons possess the machinery for glycogen synthesis, healthy neurons do not store glycogen. A main contributing factor of neuronal vulnerability to metabolic stress compared with other somatic cell types, including glia, is the absence or paucity of glycogen storage in neurons. While the bulk of brain glycogen is located within astrocytic processes, there is evidence of its localization within hippocampal and cortical neurons in animals fixed by microwave perfusion (2). Glycogen accumulation in neurons is thought to be neurotoxic as it has long been associated with Lafora disease, a neurodevelopment disorder associated with intractable epilepsy, as well as a variety of neurodegenerative diseases (3). Indeed, induced glycogen accumulation in mouse neurons leads to apoptosis and autophagy (4), leading many to speculate the neuronal glycogen synthetic machinery is silenced to prevent neurotoxicity. However, evidence also supports a more nuanced role for the physiological storage of neuronal glycogen. Rodent neurons in normal postnatal brain store glycogen as a normal part of development (5). In primary cultured neurons, glycogen metabolism confers resistance to hypoxia (6). In addition, induction of glycogen synthase (GS) in cultured neurons

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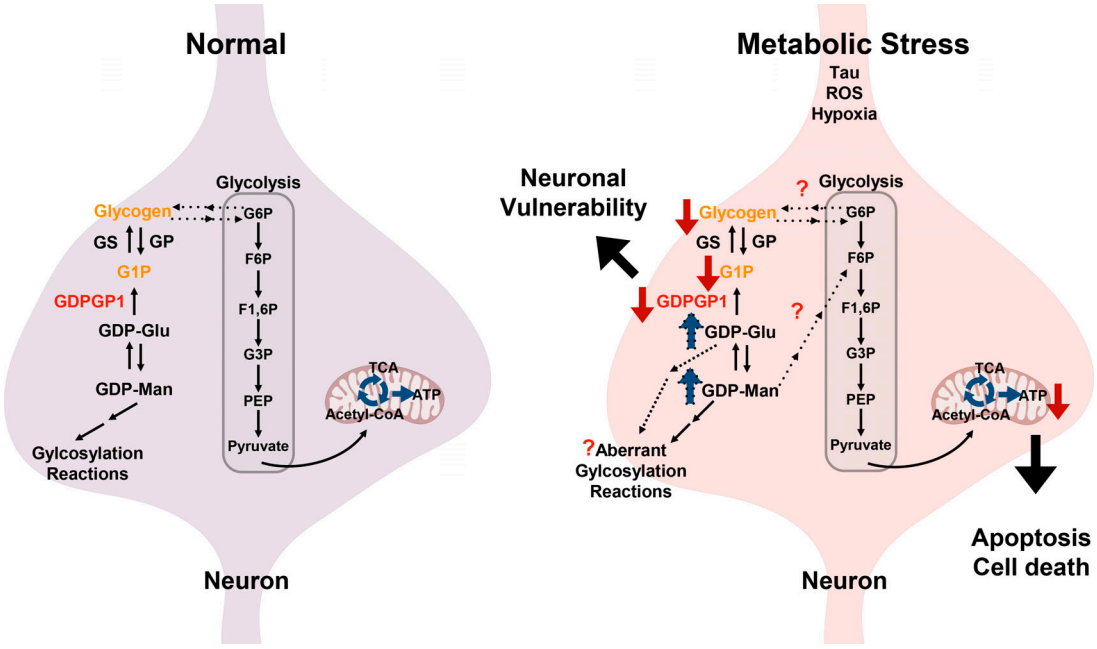

Figure 1. **Schematic of the relationship between putative neuronal glycogen metabolic pathways and established glycolytic and oxidative phosphorylation pathways in normal (left) and metabolically stressed (right) neurons.** Metabolic stressors can ultimately lead to apoptotic or necrotic cell death by causing neuronal mitochondrial dysregulation and bioenergetic failure. The work by Schulz et al. suggests that, under metabolic stress (hypoxia, reactive oxygen species [ROS], or tau aggregation), neurons exhibit vulnerability due to maladaptive down-regulation of GDPGP1 and associated reduced neuronal glycogen and G1P content (1). Future experiments will be required to further understand other cell physiological consequences of GDPGP1 down-regulation such as the potential accumulation of GDP-glucose (GDP-Glu) and aberrant glycosylation products or the possible stimulation of fructose metabolites, which could support glycolysis in the hypoxic brain. Arrows with dashed lines indicate pathways/relationships requiring further experimental evidence. G3P, glycerol 3-phosphate; G6P, glucose-6-phosphate; GDP-Man, GDP-mannose; GP, glycogen phosphorylase; GS, glycogen synthase; F6P, fructose-6-phosphate; F1,6P, fructose-1,6-bisphosphate; PEP, phosphoenolpyruvate.

expressing the Huntingtin protein reduces the aggregation of mutant protein by stimulating autophagy (7). Also supporting a functionally significant physiological effect of neuronal glycogen, mice bearing genetic deletion of glycogen synthase restricted to forebrain pyramidal neurons have impaired synaptic plasticity and learning (8).

In light of the above work, the present study raises several questions regarding the regulation and normal physiological role of GDPGP1 in neurons, and how its maladaptive down-regulation in response to stress specifically modulates glycogen and glycolytic metabolic pathways (Fig. 1). Indeed, one hypothetical adaptive function of GDPGP1 down-regulation in response to metabolic stress could be to shunt additional substrates for fructose-driven glycolysis (9). In addition, as hypothesized by others, GDPGP1 down-regulation may lead to aberrant glycosylation products containing GDP-D-glucose instead of GDP-D-mannose, which could play a role in shaping cellular responses to hypoxia (10). Mechanistic studies evaluating these possibilities as well as deciphering the transcriptional regulators linking hypoxia to GDPGP1 down-regulation will shed important light into the normal function and regulation of GDPGP1. Perhaps most intriguing and challenging will be tying in the function of GDPGP1 with the emerging role of neuronal glycogen storage as an adaptive metabolic response and its links to cellular processes, including apoptosis and autophagy. *C. elegans* remains an ideal model to answer these questions and may provide further insights into organismic coordination of glycogen metabolism, as Schulz et al. found that non-neuronal expression of *mcp-1* seemed to rescue *mcp-1* mutants in stress resistance although it did not restore glycogen levels (1).

Setting out to uncover stress-regulated genes, Schulz et al. unexpectedly identified a pathway intersecting with the long-standing puzzle of neuronal glycogen metabolism (1). Going forward, it will be key to address technical challenges including sensitive detection and quantification of neuronal glycogen and related GDPGP1 metabolite flux under stress conditions. In addition, assessing the in vivo relevance of GDPGP1 in mice or other mammalian models of ischemic and neurodegenerative diseases will be of great translational interest. While previous studies and exciting new findings from this work have laid the foundation, it will be important to further elucidate the physiological relevance of the maladaptive GDPGP1 response and the causal role of, and mechanistic basis for, neuronal glycogen metabolism in neuronal survival versus vulnerability to a variety of metabolic stresses.

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