Introduction to the Thematic Minireview Series: Brain glycogen metabolism

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The synthesis of glycogen allows for efficient intracellular storage of glucose molecules in a soluble form that can be rapidly released to enter glycolysis in response to energy demand. Intensive studies of glucose and glycogen metabolism, predominantly in skeletal muscle and liver, have produced innumerable insights into the mechanisms of hormone action, resulting in the award of several Nobel Prizes over the last one hundred years. Glycogen is actually present in all cells and tissues, albeit at much lower levels than found in muscle or liver. However, metabolic and physiological roles of glycogen in other tissues are poorly understood. This series of Minireviews summarizes what is known about the enzymes involved in brain glycogen metabolism and studies that have linked glycogen metabolism to multiple brain functions involving metabolic communication between astrocytes and neurons. Recent studies unexpectedly linking some forms of epilepsy to mutations in two poorly understood proteins involved in glycogen metabolism are also reviewed.

Glycogen has fascinated biologists for over a century due to its pivotal role in the efficient and dynamic storage of glucose molecules. Classical studies found that glucose storage as glycogen in muscle and liver is enhanced following feeding, and that these stores are rapidly degraded during exercise or fasting, respectively. Initial efforts to understand the biochemical mechanisms underlying these responses identified the key enzymes glycogen phosphorylase and glycogen synthase, and found that the activities and conformations of these enzymes are stably modified in response to hormonal signals, such as adrenaline and insulin. Mutations in the genes encoding these proteins, as well as other glycogen-metabolizing enzymes, result in an array of glycogen storage diseases that typically affect skeletal muscle and/or liver. Careful chemical analyses revealed that a key event in regulating glycogen phosphorylase is the covalent modification by phosphate. This discovery led to the initial characterization of phosphoprotein phosphatases and protein kinases. Investigations of the molecular basis for hormonal regulation of the protein kinases resulted in the detection of cAMP and development of the "second messenger" signaling concept. These findings stimulated pioneering studies that identified heterotrimeric G proteins, G protein–coupled receptors, and other second messengers. Many key papers reporting these findings were published in *The Journal of Biological Chemistry*. There is little exaggeration in stating that our collective curiosity about glucose and glycogen metabolism spawned studies conducted by multiple generations of biological chemists that have been recognized by nine Nobel Prizes in Physiology/Medicine or Chemistry.

A natural follow-up question to this brief historical overview might be: what else is there to learn about glycogen metabolism? It turns out, quite a lot. It has been well-known for many years that almost all tissues contain glycogen, albeit at significantly lower levels than found in muscle or liver. Little attention was paid to the molecular mechanisms that regulate glycogen stores in other tissues or cells, and very few studies addressed the role of glycogen itself, which was largely presumed to serve as a short-term glucose store. The first careful characterizations of glycogen in the brain were published in a series of papers by Stanley E. Kerr and colleagues that appeared in *The Journal of Biological Chemistry* during the 1930s (1, 2). Astrocytes are now known to be the predominant brain cell type containing glycogen, where it is largely distributed throughout astrocytic cytosol, endfeet, and perisynaptic processes (3–6). When compared with astrocytes, much lower levels of glycogen, glycogen phosphorylase, and glycogen synthase are present in neurons (7, 8). However, the precise role(s) of brain glycogen remain elusive.

This series of four Minireview articles provides an overview of glycogen metabolism in the brain, summarizes current thinking regarding the roles of glycogen in different cell types, and discusses the importance of glycogen to brain function. The first article, by Prats, Graham, and Shearer (9), discusses the dynamic life of the glycogen granule, with attention to control of the size and number of granules, composition of the macromolecule and its microenvironments, and its compartmentation. These authors draw on the detailed knowledge base derived from studies in liver and muscle that have not yet been

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carried out in brain. Nadeau, Fontes, and Carlson (10) review the regulation of glycogenolysis, with detailed discussion of the properties and regulatory mechanisms of the three enzymes and their isoforms involved in glycogen breakdown: phosphorylase kinase, glycogen phosphorylase, and the debranching enzyme. Besides glycogenolysis, glycogen synthesis, glycogen turnover, and the glycogen shunt are also important aspects of glycogen metabolism in the brain. Bak, Walls, Schousboe, and Waagepetersen (11) discuss roles of glycogen in normal brain functions and diseases, including its use in astrocytes with regulation by local energy demands, and glycogen mobilization during neurotransmission when receptor-mediated signaling pathways and astrocytic control of the extracellular milieu serve to integrate astrocytic glycogenolysis with neuronal activity. Gentry, Guinovart, Minassian, Roach, and Serratosa (12) review the structural abnormalities in glycogen caused by mutations in the E3 ubiquitin ligase malin and the glycogen phosphatase laforin, and describe the role of glycogen in the pathophysiology of Lafora disease, which is characterized by severe epilepsy and death.

In summary, there is a strong need for the development of an improved understanding of glycogen neurobiology. The goal of this series is to increase interest in brain glycogen research by providing a foundation to facilitate studies of the complexities of glycogen turnover in various cell types, and to attract the application of new experimental methods and approaches to study normal and pathophysiological roles of glycogen in the brain.

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