A tale of two GAGs: heparan sulfate and hyaluronan in neurophysiology and neurological disorders

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Glycosaminoglycans (GAGs) are a family of linear acidic polysaccharides, including heparan sulfate, chondroitin sulfate, keratan sulfate, and hyaluronan. GAGs are present mainly in the cell surface and extracellular matrix as proteoglycans. Physiological roles of GAGs in various tissues can be effectively studied by using conditional knockout of glycosyltransferases necessary for their synthesis. We have used this approach to determine the roles of GAGs in the nervous system. Earlier studies have established the essential roles of heparan sulfate in various aspects of brain development. More recently, we have applied this approach to investigate the role of GAGs in neurophysiology, cognition, and behavior. This line of studies has revealed unexpected roles of GAGs in the pathogenesis of neurological and mental disorders. For instance, the removal of heparan sulfate from excitatory neurons results in striking recapitulation of the constellation of autism-like behavioral phenotypes, which is correlated by reduced surface expression of glutamate receptors in excitatory synapses. On the other hand, mutant mice lacking hyaluronan synthase genes display spontaneous epileptic seizures.