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PERSPECTIVES

Vertebrate galectins: endogenous regulators of ionotropic glutamate receptors?

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Lectins are proteins that bind specific carbohydrate residues on glycoproteins and glycolipids. In many cases, such binding alters the functional properties of the targeted protein or lipid and triggers a change in cell physiology. First characterized in plants, lectins with diverse carbohydrate specificity have subsequently been identified in animals, where they serve a variety of different functions including both intracellular regulation of protein sorting and extracellular interactions with carbohydrate moieties on the cell surface and in the extracellular matrix (Dodd & Drickamer, 2001). Both plant and animal lectins typically exist as dimers or multimers with their biological action being dependent on, or enhanced by, the ability to form cross links between protein subunits. In the case of ionotropic glutamate receptors (iGluRs) early work with plant lectins demonstrated a potentiating action on agonist-evoked currents recorded in insect and vertebrate cells. Vertebrates express three distinct iGluR families, but only α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate (KA) subtypes exhibit strong direct modulation by lectins while *N*-methyl-D-aspartate (NMDA) receptors are relatively unaffected. Brief exposure to wheat germ agglutinin, concanavalin A (ConA) or isolectin B4, with specificity for *N*-acetylglucosamine, mannose and β-galactosides, respectively, increases the amplitude of steady-state currents evoked via KA and/or AMPA receptors (Mayer & Vyklicky, 1989; Huettner, 1990).

Now, a study from Geoff Swanson's lab in this issue of *The Journal of Physiology* (Copits *et al.* 2014) investigates the ability of vertebrate galectins, including recombinant human galectin-1, and congerin I and II from the conger eel, to regulate native and recombinant AMPA and KA receptors. Galectins bind specifically to β-galactoside glycoconjugates and the three galectins studied by Copits *et al.* (2014) can each form a bivalent homodimer. In contrast to tetravalent ConA, which substantially increases currents mediated by most AMPA and KA receptor isoforms, galectin application produced a remarkable diversity of effects on recombinant iGluRs depending on the specific subunits that were expressed and on which galectin was applied. For example, congerin caused a substantial slowing of AMPA receptor desensitization with an increase in steady-state current in cells expressing homomeric GluA4 and some of the cells expressing GluA1 whereas human galectin-1 had a greater effect on GluA1 than GluA4. In addition, congerin, but not galectin-1, reduced peak current with little change in kinetics in cells that expressed homomeric GluA2 or the GluA1/GluA2 heteromeric combination. Similarly, both eel and human galectins elicited a significantly greater slowing of desensitization in homomeric GluK2 KA receptors than homomeric GluK1 or heteromeric GluK2/GluK5 combinations. Modulation persisted in heterologous cells that were co-transfected with AMPA or KA receptor subunits together with their auxiliary subunits stargazin or Neto2, respectively.

Mechanistically, galectin modulation of GluK2 was reduced by drugs that interfere with oligosaccharide processing and prevented by point mutations that eliminate three essential glycosylation sites at the interface between the receptor's amino terminal and ligand binding domains (Everts *et al.* 1999). In addition, GluK2 modulation was enhanced by linkers that stabilized the recombinant galectin as an obligate dimer, which is consistent with the idea that iGluR modulation involves crosslinking subunits via their attached glycoconjugates. In future work, it would be interesting to determine whether galectin–3, which can assemble into a pentameric oligomer, might elicit even stronger modulation.

When tested on neuronal AMPA receptors in cultures prepared from rat hippocampus, congerin failed to change the amplitude or time course of agonist-evoked or spontaneous excitatory synaptic currents, possibly owing to additional modifications of glycoconjugates in central neurons that render them resistant to galectins or, alternatively, prior occupation of the binding site by endogenous lectins produced in the cultures that occlude the binding of acutely applied exogenous galectin. On the other hand, both congerin and human galectin-1 slowed desensitization of KA receptor-mediated currents recorded in freshly dissociated mouse sensory neurons, cells that are known to express galectin-1 and -3 as well as β-galactoside glycoconjugates (Jessell *et al.* 1990). Thus, Swanson and colleagues (Copits *et al.* 2014) have established the potential for native receptors to be modulated by endogenous lectins, but much work remains to determine where and when such regulation actually occurs.

Mice lacking galectin-1 are viable but exhibit changes in primary afferent morphology and sensitivity (McGraw *et al.* 2005) as well as resistance to death of central neurons subsequent to pilocarpine-induced seizures (Bischoff *et al.* 2012). Whether or not these phenotypes involve alteration in iGluR modulation remains to be determined, but the availability of both galectin–1 and galectin–3 knock-outs should aid in unravelling their potential role in regulating excitatory amino acid receptors.

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Additional information

Competing interests

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