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# CARBOHYDRATES AND CARBOHYDRATE–BINDING PROTEINS IN THE NERVOUS SYSTEM

*T. M. Jessell,* M. A. Hynes,* and J. Dodd†*

Center for Neurobiology and Behavior, Departments of *Biochemistry and Molecular Biophysics, Howard Hughes Medical Institute, and †Physiology and Cellular Biophysics, Columbia University, New York, New York 10032

## INTRODUCTION

The possibility that cellular interactions within the vertebrate nervous system are mediated by cell surface carbohydrates has been considered on numerous occasions. The initial suggestions that carbohydrate structures might mediate neural cell adhesion were based on the expression of complex oligosaccharides, in particular gangliosides, by neural cells, and the detection of cell surface glycosyltransferases that were proposed to function nonenzymatically as receptors for surface oligosaccharides (Roseman 1970, Roth et al 1971, Marchase 1977, Shur & Roth 1975). Subsequent progress in elucidating the function of cell surface carbohydrates in the nervous system has, however, been slow, in part because of the difficulties (*a*) in purifying and characterizing complex oligosaccharides that are expressed on small subsets of neural cells and (*b*) in generating these structures synthetically. In addition, the identification of cell surface molecules such as neural cell adhesion molecules (NCAM), N-cadherin, and integrins (Edelman 1986, Takeichi 1988, Ruoslahti & Pierschbacher 1987, Rutishauser & Jessell 1988) has focused attention on mechanisms of neural cell adhesion that involve direct protein-protein interactions.

Increasing evidence indicates that interactions between surface oligosaccharides and carbohydrate-binding proteins mediate cell adhesion and recognition between nonneural cells. Thus, the stage- and species-specific

binding of a sperm to the zona pellucida coat that surrounds mammalian oocytes has been shown to result from the interaction of a sperm receptor with an O-linked oligosaccharide that is present on the zona pellucida glycoprotein, ZP-3 (Wassarman 1987). Evidence also indicates that the polylactosamine oligosaccharides present on the blastomeres of pre-implantation mouse embryos are involved in adhesive interactions that occur during compaction (Fenderson et al 1984, Rastan et al 1985, Bayna et al 1988). In addition, the specific homing of recirculating lymphocytes to peripheral lymphoid targets (Rosen et al 1985, Rosen & Yednock 1986, Gallatin et al 1986, Brandley et al 1987) appears to depend, at least in part, on receptors that recognize specific carbohydrate structures. Finally, the hepatic asialoglycoprotein receptor that is responsible for the clearance of circulating serum glycoproteins (Ashwell & Harford 1982) represents the best-characterized surface protein with a defined physiological role in the recognition of carbohydrate structures.

With the availability of monoclonal antibodies (MAbs), the complex expression patterns of oligosaccharides on neural cells has become more readily apparent. Some of the defined carbohydrate antigens are highly restricted to subsets of vertebrate neurons and reveal molecular gradients in developing neural tissues. In addition, several carbohydrate-binding proteins with specificity for neural cell surface oligosaccharides have recently been detected in the vertebrate nervous system. In this review we discuss briefly the evidence emerging from both neural and nonneural systems that indicates that cell surface carbohydrate structures may indeed play important roles in mediating neural cell recognition and adhesion.

## DIVERSITY OF CARBOHYDRATE STRUCTURES ON VERTEBRATE CELLS

The complex oligosaccharides expressed by vertebrate cells are associated with ceramides in glycolipids or attached via N- or O-linkages to protein backbones. Several classes of carbohydrate structures can be defined on the basis of their polysaccharide backbone sequences (Table 1). Lactoseries

**Table 1** Oligosaccharide classification by polysaccharide backbone sequence

| | |
|---|---|
| Lactoseries | |
| (Type 1) | Gal(β1-3)GlcNAc(β1-3)Galβ1-4Glc-R |
| (Type 2) | Gal(β1-4)GlcNAc(β1-3)Galβ1-4Glc-R |
| Globoseries | GalNAcβ1-3Galα1-4Galβ1-4Glc-R |
| Ganglioseries | Galβ1-3GalNAcβ1-4Galβ1-4Glc-R |

carbohydrates contain the [Gal$\beta$1-3(4)GlcNAc-R] structure, globoseries carbohydrates contain the [GalNAc$\beta$1-3Gal$\alpha$1-4Gal-R] backbone and ganglioseries structures contain the [Gal$\beta$1-3GalNAc$\beta$1-R] sequence (Hakomori 1981, Feizi 1985). These backbone sequences can be modified extensively by the addition of branched or terminal saccharides, thus generating many structurally distinct members of each class. In addition, the attachment of the same saccharide via multiple linkages, the existence of branched carbohydrate chains of the same or differing structure, and extensive variation in sialic acid content (Schauer 1982) provide the potential for an enormous diversity of complex oligosaccharide structures.

The assembly of complex oligosaccharides is achieved by the coordinated and sequential activity of glycosyltransferase enzymes (Beyer & Hill 1982). Each enzyme is capable of adding specific saccharides via defined linkages to a highly restricted set of oligosaccharide substrates. The structural diversity in cell surface oligosaccharides must therefore be defined in large part by the cellular expression and substrate specificity of these glycosyltransferases.

## CARBOHYDRATE-BINDING PROTEINS

A large number of endogenous proteins have been characterized that bind to distinct surface oligosaccharides on vertebrate cells. These carbohydrate-binding proteins can be subdivided into several categories on the basis of their primary structure and biochemical properties (see Drickamer 1988, Barondes 1988):

1. Calcium-dependent carbohydrate-binding proteins (C-type lectins): Lectins of this class require the presence of calcium for carbohydrate-binding activity and are defined on the basis of the homology with the carbohydrate-recognition domain of the rat hepatic asialoglycoprotein receptor (Drickamer 1988). The common structural organization of the binding domain results from a conserved set of 18 amino acids that includes cysteine residues involved in disulphide bond formation, which is essential for carbohydrate-binding activity (Drickamer 1988). Different members of this class exhibit distinct sugar-binding specificities that may result from nonconserved amino acids within the binding domain. This class of lectins also includes the chicken hepatic *N*-acetylglycosamine receptor, the soluble rat mannose-binding proteins (Drickamer et al 1986, Ezekowitz et al 1988), the pulmonary surfactant apoprotein (Haagsman et al 1987), cartilage proteoglycan (Krusius et al 1987, Halberg et al 1988), and a lymphocyte homing receptor (Siegelman et al 1989, Lasky et al 1989). Several other proteins have been identified that exhibit this conserved carbohydrate-binding domain but that have not yet been demonstrated to function as lectins.

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