

A spoonful of sugar to control inflammation?

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Research Article

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The therapeutic use of sugars is a familiar concept in microbial pathogenesis. Lectin-mediated adhesion to eukaryotic cells has been recognized as critical to the initiation of infection by viruses since the 1940s and by bacteria since the 1960s. Susceptibility to infection can depend on the display of an attractive carbohydrate ligand on mucosal surfaces, as is known for cholera, urinary tract infection, or whooping cough. Once lectin-carbohydrate binding was understood at the molecular level, it became possible to show that competitive inhibition of adherence by sugars would eliminate the pathogen. For example, sugars in breast milk protect against pathogens of infancy, and soluble carbohydrates can wash away mucosal pathogens in vivo (1, 2).

For eukaryotic cell systems, the demonstration of lectins as recognition molecules was a more recent event (3). However, a research effort of staggering scale has made up for lost time and these molecules are now known to provide information for cellular trafficking, development, inflammation, neoplastic transformation, and cell-cell adhesion. Following the example of the prokaryotic spies, it has become obvious that subsets of lectin-mediated adhesion systems can be determinants of disease, raising the possibility of using lectins or carbohydrates to competitively inhibit pathological adhesion. A particularly attractive target for this approach is the selectin-dependent rolling of leukocytes at sites of inflammation (4, 5). In this issue of *The Journal*, Granert et al. (6) have demonstrated the principle that a soluble carbohydrate can interfere with leukocyte trafficking in vivo.

Granert et al. (6) chose as their test system the rabbit model of meningitis, which has several outstanding advantages for the demonstration of antiinflammatory effects. The model measures the movement of leukocytes across the cerebral capillary endothelium into the fluid compartment of the subarachnoid space. The ease of sampling this fluid multiple times in the same animal allows for the construction of a time course of inflammation in each subject. Accumulation of serum proteins in cerebrospinal fluid serves as a marker of injury in the system. It is well established that leukocyte transmigration is an important contributor to injury in experimental and clinical meningitis (for reviews see references 7 and 8). Thus, the demonstration of inhibition of pleocytosis in cerebrospinal fluid in this model is likely to indicate a medically relevant therapeutic effect.

Leukocyte transmigration into the brain has been shown to involve selectins, CD18 integrins, ICAM-1, and VCAM (9-11). In the rabbit model of acute bacterial meningitis, inhibition of E- or P-selectin or the CD18 integrins by peptide analogues or antibodies effectively decreases leukocyte recruitment into cerebrospinal fluid and, in parallel, decreases blood-brain barrier injury (10, 12). Thus, inhibition of either leukocyte rolling or adhesion has proven to be antiinflammatory in the central nervous system in vivo. The novelty of the Granert et al. (6) study is the use of a sugar as inhibitor and L-selectin as the target. L-Selectin on circulating leukocytes

recognizes sialylated, fucosylated polylactosamines on endothelial cells leading to the margination and rolling of the leukocytes in an obligatory step before leukocyte extravasation. Anti-L-selectin antibodies block leukocyte trafficking to lymph nodes and leukocyte accumulation during peritoneal inflammation (13). Fucoidin, a large polymer of L-fucose and L-fucose-4-sulphate, has been shown to be a potent inhibitor of L-selectin binding to endothelial ligands. These findings set the stage to determine if intravenous administration of a sugar analogue of a selectin target, in this case fucoidin, would result in a therapeutic decrease in inflammation in the brain. Granert et al demonstrated that fucoidin caused a generalized loss of leukocyte rolling (confirmed by intravital microscopy in muscle) and profoundly inhibited leukocytosis in skin and cerebrospinal fluid. This series of experiments unequivocally demonstrates the principle that a sugar analogue of a selectin target can block inflammation in brain and peripheral sites in vivo.

There are several questions remaining before this approach can be designated viably therapeutic. The inhibition of leukocyte recruitment achieved in these experiments was sufficient to block the enhanced blood-brain barrier permeability seen in meningeal inflammation but the effect on lactate accumulation, a marker of cerebral ischemia, was less impressive. Thus, it is not as yet possible to predict if fucoidin will be sufficiently protective so as to enhance survival by controlling the burst of inflammation that occurs during antibiotic treatment of natural meningitis (8). It is likely that the serum concentration of a sugar analogue will have to be maintained at fairly high levels to be therapeutic since soluble selectins shed from activated cells circulate in blood and will presumably divert a significant portion of the circulating sugar from the cell-bound target. The optimal sugar for such a selectin competitor would need to be of high affinity (i.e., multivalent like fucoidin), of high purity, and available in large quantities. The efficacy of fucoidin might also depend in part on its ability to block not just the L-selectin, but also the P- and E-selectins. The choice of L-selectin for the target of inhibition in acute inflammation may suffer a secondary disadvantage, in that this molecule is the determinant of lymphocyte homing. Lymphocyte homing does not contribute to acute meningeal inflammation but is presumably important to antigen processing in the development of protective immunity against the offending infection and therefore should be left intact. As selectin biology moves from the bench into in vivo systems such as the meningitis model, the therapeutically optimal match of organ, disease, and lectin-carbohydrate competitor will eventually be distinguished.

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