Form Determines Function

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A team of researchers at the Universities of Bielefeld and Hamburg (Germany) has now produced cyclopeptides that imitate the HNK-1 carbohydrate from human natural killer cells.

HNK-1 is involved in many developmental biological processes of the nervous system. It boosts motor neuron axon growth, the growth of the fibers of muscle nerve cells. HNK-1 is found along the routes used by nerve fibers after an injury to peripheral nerves.

Carbohydrates play an important role in a broad spectrum of physiological as well as pathological processes. For example, polysaccharides on the surface of tumor cells or pathogens are possible points of attack for therapeutic drugs or vaccinations. However, the synthesis of carbohydrate-based drugs or vaccines has proven to be very complex. In addition, these are not easily absorbed into the body and decompose far too quickly. Cyclopeptides (short ring-shaped protein chains) called glycomimetics, which imitate polysaccharides in form and consequently in function, could be a useful alternative. They are easy to produce, relatively stable, and easily absorbed.

As a first step, the researchers led by Norbert Sewald (Bielefeld) and Melitta Schachner (Hamburg) combed through a very large number of linear peptide chains with random amino acid sequences, searching for peptides that could be recognized by HNK-1 antibodies. Starting with the sequences of two such peptides, they synthesized a series of different cyclic hexapeptides. Their trick was to replace one L-amino acid in each cyclopeptide with its corresponding D-amino acid. L-amino acids are the

form that occurs in nature, D-amino acids are their mirror image. Whereas a “normal” cyclic hexapeptide is very flexible, constantly changing its spatial structure, a D-amino acid component stabilizes one preferred conformation of the ring. The peptide “presents” its functional groups of atoms in a predictable three-dimensional arrangement that is further determined by the position of the D-amino acid. The amino acid L-proline has a similar stabilizing effect; so cyclic hexapeptides containing this unit were also tested.

Sewald and his team identified several interesting candidates based on their tendency to bind to antibodies against HNK-1. They then took a closer look at a few of these. Trials with motor neuron cell cultures demonstrated that two of the mimetics tested did indeed stimulate axon growth. Indeed, they were more effective than the linear peptide chains the researchers started with. Structural analyses and computer simulations identified a particular spatial structure of the cyclopeptides as being crucial to their effectiveness.

Substances able to support the regeneration of axons after injuries could be a highly promising starting point for developing a treatment of patients with spinal cord injuries. These new cyclopeptides could be a step in the right direction.

Source: Universität Bielefeld