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# Researchers discover molecule responsible for axonal branching

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The human brain consists of about 100 billion (1011) neurons, which altogether form about 100 trillion (1014) synaptic connections with each other. A crucial mechanism for the generation of this complex wiring pattern is the formation of neuronal branches. The neurobiologists Dr. Hannes Schmidt and Professor Fritz G. Rathjen at the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, have now discovered a molecule that regulates this vital process. At the same time they have succeeded in elucidating the signaling cascade induced by this molecule.

Through the ramification of its fiber-like axon, a single neuron can send branches and thus transmit information into several target areas at the same time. In principle, neurobiologists distinguish between two kinds of axonal branching: branching of the growth cone at the tip of an axon and the sprouting of collaterals (interstitial branching) from the axon shaft.

Both forms of axonal branching can be observed in sensory neurons, which transmit the sensation of touch, pain and temperature, among others. When the axons of these neurons reach the spinal cord, their growth cones first split (bifurcate) and consequently the axons divide into two branches growing in opposite directions. Later new branches sprout from the shaft of these daughter axons which penetrate the gray matter of the spinal cord.

Through investigations on sensory neurons, Dr. Hannes Schmidt and his colleagues were able to identify a protein which triggers the splitting of

the growth cone of the sensory axons: the peptide CNP (the abbreviation stands for C-type natriuretic peptide). In transgenic mice the scientists were able to show that CNP is formed in the spinal cord precisely when sensory neurons grow into it. In the absence of CNP bifurcation can no longer occur which results in reduced neuronal connectivity in the spinal cord.

The new findings supplement earlier discoveries of the research group of Professor Rathjen according to which a cGMP-signaling cascade is responsible for the bifurcation of sensory axons. When CNP binds to its receptor Npr2 (natriuretic peptide receptor 2) on the surface of the axons, this signaling cascade is set in motion, which in turn induces the formation of the secondary messenger molecule cGMP. This messenger molecule then activates the protein kinase cGKI (cGMP-dependent protein kinase I), which can switch on and off a whole series of target proteins. The cytoskeleton of the neurons is thus altered in such a way that their growth cone splits into two daughter axons.

Next, the researchers want to identify these target proteins. Further analyses should clarify whether the cGMP signaling cascade likewise regulates the branching of other axon systems and whether this impacts the sensation of pain.

More information: C-type natriuretic peptide (CNP) is a bifurcation factor for sensory neurons, *PNAS*, Early Edition, 2009, doi:10.1073

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