dopamine that was released in the nucleus accumbens in response to morphine was greatly reduced, and injection of plasmin into the nucleus accumbens in *tPA*^{-/-} mice reversed this effect.

So, the authors propose that morphine causes an increase in tPA in the nucleus accumbens, which converts plasminogen to plasmin and thereby leads to an increase in the release of dopamine. The pathway that leads from plasmin production to dopamine release is unknown, but it could be related to the degradation of laminin (an extracellular matrix protein that regulates calcium channels at synapses) by plasmin. Future work should focus on elucidating this pathway.

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References and links

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GLIA

Myelin made to measure

There is a precise and predictable relationship between the diameter of an axon and the thickness of the myelin that surrounds it. Writing in *Science*, Michailov, Sereda and colleagues describe evidence that the amount of neuregulin-1 (Nrg1) that is produced by an axon tells Schwann cells how thick the myelin sheath around that axon should be.

The speed at which action potentials are conducted along an axon depends largely on the diameter of the axon and the thickness of its myelin sheath — two factors that are closely related. Maintaining the precise control of conductance velocity is essential for the proper function of the nervous system, and it has been suggested that myelin thickness might be controlled by interactions between ligands produced by the axon and receptors on the myelinating glia. Michailov *et al.* tested the idea that the axonal ligand that is responsible — in the periphery, at least — is Nrg1, interacting with ErbB receptors on Schwann cells.

The *Nrg1* gene is expressed in neurons of the sciatic nerve in mice, and *ErbB2* and *ErbB3* are expressed by Schwann cells. If interactions between Nrg1 and ErbB receptors control myelin thickness, changes in the amount of ligand or receptor might alter the thickness of the myelin sheath. When the authors generated compound heterozygote mice that had reduced gene dosages of both *Nrg1* and *ErbB2*, they found that the myelin in the sciatic nerves of the mice was significantly thinner than usual. Although the mice seemed normal, the conduction velocity in their nerves was also reduced, even though the sizes of the axons were unchanged.

To narrow down the cause of the reduced myelination, the authors looked at mice with reduced dosages of just the *Nrg1* gene or the *ErbB2* gene. Mice that were heterozygous for *ErbB2* showed normal myelination, but in the *Nrg1* heterozygotes, the myelin was as thin as in the compound heterozygotes. So the expression of Nrg1 seems to control the thickness of myelin.

To test this theory further, the authors generated mice in which Nrg1 was overexpressed under the control of the murine Thy1.2 promoter, so that the excess Nrg1 was expressed specifically in post-natal motor neurons and dorsal root ganglion neurons. In these mice, the peripheral nerves showed hypermyelination when compared with wild-type mice.

There are three isoforms of Nrg1, and these effects seem to be specific for Nrg1 type III. Mice that overexpressed Nrg1 type III showed

hypermyelination, but mice that overexpressed Nrg1 type I did not (although they did show some myelin abnormalities in the CNS). A specific reduction in the expression of the Nrg1 type III isoform also produced hypomyelination, indicating that Nrg1 types I and II cannot compensate for the lack of the type III isoform.

These results support a model in which Nrg1 type III is produced as a function of axonal diameter. The amount of Nrg1 dictates the amount of signalling through the Schwann cell ErbB receptors, and this controls the degree of myelination of each axon. Important questions include how the production of Nrg1 is quantitatively controlled, and what signalling pathway is responsible for dictating myelin thickness as a result.

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References and links

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WEB SITE

Nave laboratory: <http://nave.em.mpg.de/root/>