REPAIR

High cAMP keeps neurons young

In mammals, embryonic neurons can regenerate, but in the central nervous system (CNS), this ability is lost as neurons mature during early postnatal development. Recreating the embryonic environment in the adult CNS might therefore help to promote repair following injury. One factor that inhibits regeneration is myelin, and modifying myelin itself might create a more permissive environment for neuronal regeneration. However, an alternative approach that is being explored is the modulation of the neuronal response to myelin. As Cai *et al.* report in the *Journal of Neuroscience*, myelin is not inherently inhibitory, and it can even promote axonal growth in embryonic and neonatal neurons. What causes this switch in responsiveness? And could adult neurons be induced to behave like their embryonic counterparts?

The authors previously reported that elevating the levels of the cyclic nucleotide cAMP in adult neurons enables them to regenerate their axons in the presence of myelin. In this new study, they examined whether endogenous cAMP levels change during development, and whether this might mediate the change in responsiveness to myelin. They showed that, in rat dorsal root ganglion (DRG) neurons, the cAMP level drops during early postnatal development, coinciding with the period in which these neurons lose their ability to regenerate.

The authors also tested the response of DRG neurons to an inhibitory component of myelin, myelin-associated glycoprotein (MAG). Normally, MAG promotes neurite outgrowth from neonatal DRG cells. However, if a downstream cAMP effector — protein kinase A — is blocked, these cells can no longer regenerate in response to MAG. By contrast, raising the level of cAMP in adult DRG neurons causes them to behave more like neonatal cells, as they now extend neurites in the presence of MAG.

So, for the first time, a three-way connection has been established between cAMP levels, the age of the neuron and its regenerative response to myelin. This confirms that raising cAMP levels in adult neurons causes them to behave as if they were much younger. If CNS regeneration is to be achieved in the adult, it seems that neurons should definitely not be encouraged to act their age!

Heather Wood

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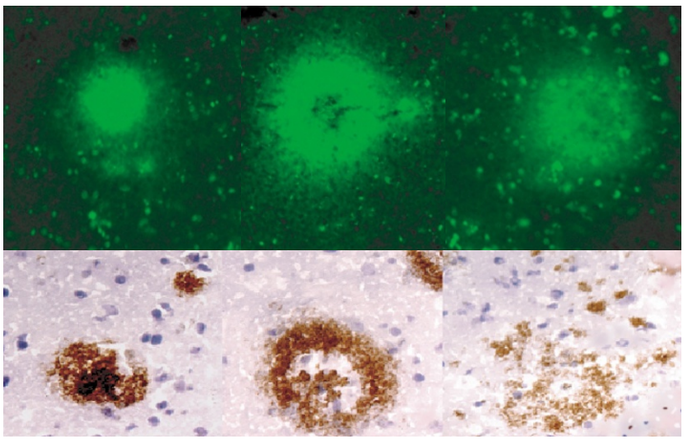

β-Amyloid (Aβ) deposits visualized in adjacent sections of Alzheimer's-disease-affected cortex by Aβ immunohistochemistry (lower panel) and using a fluorescent marker (TSQ) for zinc (upper panel). Courtesy of A. I. Bush, Harvard Medical School, Massachusetts, USA.

NEURODEGENERATIVE DISORDERS

A solution to Alzheimer's disease?

Alzheimer's disease (AD) is characterized by the accumulation of β-amyloid peptide (Aβ) in the neocortex and other brain regions; preventing or reversing the build-up of this peptide could be central to the effective treatment of the disorder. Aβ has high- and low-affinity binding sites for Cu^{2+} and Zn^{2+} — ions which are elevated in the neocortex of AD patients, particularly in amyloid plaques. The binding of Cu^{2+} and Zn^{2+} to Aβ is thought to mediate its reversible precipitation and its resistance to proteases. For this reason, Cu/Zn chelators have clear potential as a treatment for AD, as Cherny and colleagues report in *Neuron*.

In a previous study, Cherny *et al.* showed that Cu/Zn chelators can solubilize Aβ in post-mortem brain tissue from AD patients. In view of these promising results, they went on to examine the effects of a bioavailable (lipophilic) Cu/Zn chelator — clioquinol — on Aβ deposits in a transgenic mouse model (APP2576) of AD. Like other Cu/Zn-selective chelators, clioquinol could inhibit and reverse the Cu/Zn-mediated aggregation of synthetic Aβ *in vitro*, and could solubilize Aβ deposits in post-mortem AD brain samples. In transgenic mice with advanced Aβ deposition, the oral administration of clioquinol for as little as nine weeks was associated with significantly lower levels of sedimentable Aβ per wet weight of cerebral tissue, accompanied by an increase in the quantities of soluble Aβ. A decrease in amyloid plaque surface area was also observed in clioquinol-treated animals, and serum levels of Aβ were found to be lower in these mice compared with sham-treated controls. Treatment with clioquinol did not seem to be associated with any adverse reactions; in fact, the authors reported a significant improvement in scores on a general behaviour rating scale.

Cherny *et al.* argue that the effects of clioquinol contrast favourably with those of other candidate treatments tested in transgenic mouse models of AD, including the Aβ vaccination approach. In particular, they point to the relatively large reduction in the absolute quantities of Aβ after clioquinol treatment, and to the speed with which this drug achieves its beneficial effects. They suggest that clioquinol or its derivatives be investigated further as a means of treating or preventing the disorder. Important issues that will need to be addressed include the possibility that increased levels of soluble Aβ might also contribute to pathophysiology in AD. A phase II clinical trial of clioquinol in AD patients is now in progress.

Rebecca Craven

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