SPINAL CORD

Ephrins take control

Two new studies shed light on the functions of the Eph receptor tyrosine kinases and their ephrin ligands in the spinal cord. The data highlight roles in pain processing and the control of locomotion, an understanding of which might contribute to the development of therapies for chronic pain and spinal cord injury.

Recently, interactions between EphB and NMDA (*N*-methyl-D-aspartate) receptors were shown to regulate synaptic plasticity at glutamatergic synapses in the hippocampus. As NMDA receptors are also key mediators of plasticity in pain-processing regions of the spinal cord, Battaglia and colleagues wondered whether EphB receptors might have a regulatory role in nociceptive pathways.

Activation of postsynaptic EphB receptors on dorsal horn neurons by intrathecal injection of ephrinB2 coupled to an Fc antibody fragment induced thermal hyperalgesia in adult wild-type rats. Pretreatment with an NMDA receptor antagonist prevented the development of hyperalgesia in ephrinB2–Fc-injected rats, indicating that EphB receptors modulate synaptic transmission through NMDA receptors. Co-precipitation of increased amounts of phosphorylated Src with EphB receptors in ephrinB2–Fc-treated rats implied a role for the Src kinase family in the signalling pathway between EphB and NMDA receptors.

Interactions between NMDA and Eph receptors might also contribute to the control of locomotion, according to a report by Kullander *et al.* in *Science*. Addition of serotonin and NMDA to isolated spinal cords of newborn mice produced rhythmic, left-to-right alternating activity in the lumbar segments that control limb movement. By contrast, outputs from the cords of mutant mice lacking either

NEUROBIOLOGY OF REWARD

Gambling on dopamine

Dopamine neurons in the midbrain are thought to produce an error signal that could be important for learning to predict a reward. Now, it seems that the same neurons also signal the level of uncertainty in an experimental trial — which might even give us insight into why gambling is such a popular way to get rid of excess wealth.

Fiorillo and colleagues, writing in *Science*, describe experiments in which monkeys were conditioned with different visual stimuli, each of which had a different probability of being followed by a reward (a few drops of tasty fruit juice). So, for example, one of the stimuli was always followed by juice, whereas another was followed by juice on only a quarter of the trials. The monkeys learned these relationships — they would lick vigorously at the juice spout when they saw the 'always rewarded' stimulus, and the amount of licking decreased with the probability of reward.

Consistent with earlier work by the same group, dopamine neurons in the monkeys' midbrains produced a stimulus-related signal that was stronger for stimuli that predicted reward more reliably, and a reward-related signal that was stronger when reward had not been reliably predicted. But the authors also saw a new signal — a more gradual increase in firing during the two-second interval between the onset of the stimulus and the potential reward that was greatest when there was the most uncertainty about whether a reward would be forthcoming.

When a stimulus is either always or never associated with reward, there is no uncertainty. By contrast, uncertainty is greatest when the probability of reward is 0.5, and this was when the sustained response of the dopamine neurons was the greatest. So it seems that, over the course of a trial, the same population of neurons codes two different aspects of the likelihood of reward: one that corresponds to the reward prediction error (shown previously by Waelti *et al.*), as proposed in formal learning theory by Rescorla and Wagner, and another that measures uncertainty.

This second signal also has correlates in learning theory. According to the Pearce–Hall theory, attention depends on uncertainty about reinforcers, and learning depends on attention. In a real situation, an animal's uncertainty about whether an action or event will be rewarding might just mean that the animal has insufficient information on which to base a prediction — so it will pay off to attend closely to the outcome. The dopamine neurons could be providing a signal that facilitates attention, and therefore learning.

Dopamine is closely associated with reward and addiction. The gradual increase in dopaminergic signalling in the presence of uncertainty might not be reinforcing, but if it is it could explain laboratory findings that animals prefer variable reward schedules over fixed ones. It could also, according to the authors, explain why gambling — in which rewards are, by definition, uncertain, and which is hard to explain by other means — is so popular and can even seem to be addictive.

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the EphA4 receptor or ephrinB3 did not alternate rhythmically, but tended towards an abnormal synchronous pattern that results in the rabbit-like gait of these mutants. *EphA4*-null mice exhibited aberrant projection of fibres across the midline of the cord, indicating that correct wiring of the neuronal networks that control locomotion relies on recognition of ephrinB3 in the midline by EphA4 receptors.

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WEB SITE

Encyclopedia of Life Sciences:
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NEURODEGENERATIVE DISORDERS

Fighting fire with fire

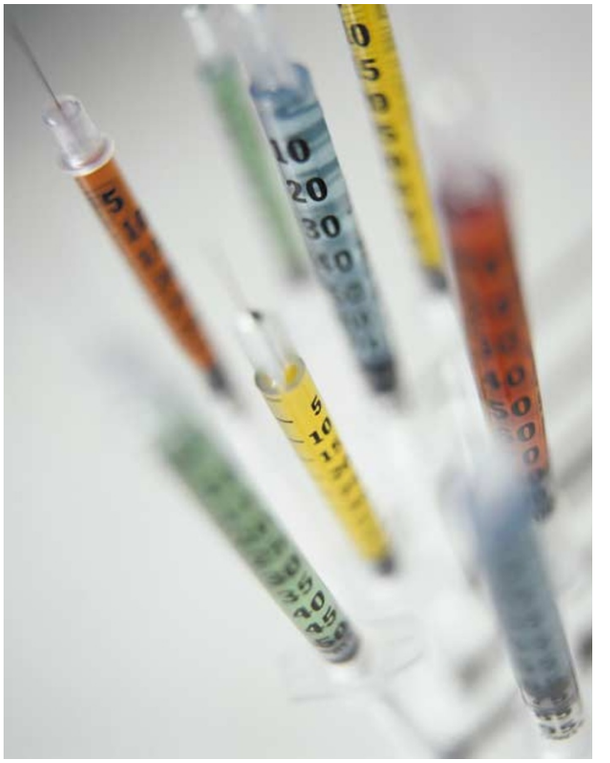
Since the pioneering work of Edward Jenner in the late 1700s, the idea of creating immunity to disease by challenging the immune system with a pathogenic agent has formed the basis for numerous successful immunization programmes. Research in mice has indicated that Alzheimer's disease (AD) might be amenable to this approach, although clinical trials were halted because of potentially serious side effects. However, despite this setback, some encouraging findings have emerged, as Nicoll and colleagues now report in *Nature Medicine*.

Their paper describes the case of a 72-year-old woman with a five-year history of AD. The woman was immunized with amyloid-β (Aβ) peptide — one of the main constituents of the plaques that accumulate in the brains of patients with AD. Previous studies in mice had shown that immunization with Aβ caused animals to mount an immune response against the endogenous peptide, leading to breakdown of many of the plaques. The mice also showed evidence of cognitive improvement — one of the principal goals of any AD therapy.

As the new paper illustrates, the human trials seemed to be considerably less successful than their animal counterparts. The woman described by Nicoll *et al.* showed no obvious signs of improvement in her AD symptoms, and several months into the trial, her overall condition deteriorated rapidly. Like several other patients that received the vaccine, she showed signs of brain inflammation. Twenty months after the start of the treatment — and twelve months after she received her last injection — she died from a pulmonary embolism. The trial was terminated at the beginning of 2002.

The prospects for the vaccine looked bleak at this stage. However, a *post mortem* examination has now shown that the woman's brain contained significantly fewer plaques than would be expected for a person at this stage of the disease. Moreover, some of the remaining Aβ was associated with microglia — the cells that are believed to be important for clearing Aβ from the brain — implying that removal of Aβ might still have been taking place at the time of her death.

So, what does the future hold for the Alzheimer's vaccine? These new findings seem to indicate that it is worth pursuing, but the side effects will clearly need to be resolved. One problem with the Aβ vaccine is that it seems to provoke a T-cell-mediated immune response, which results in a harmful encephalitis. The T-cell response might be bypassed by immunizing with antibodies against Aβ, rather than with the peptide itself. Alternatively, as the Aβ epitope that elicits the strongest immune response is in the amino terminus, it might be preferable to immunize with a fragment of Aβ instead of the full peptide. Assuming that the problems can be ironed out, it will be necessary to show that the vaccine can actually relieve the symptoms of AD in humans, or even prevent them if administered before the disease process starts. This is important both from a clinical and a research perspective — it is widely believed that amyloid plaques are at least partly responsible for the cognitive decline in AD, and the vaccine has the potential to allow the further exploration of this idea.



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