WEB WATCH

Blind prejudice

- Colour Blindness (Andrew Oakley) http://www.delamare.unr.edu/cb/
- Firelily Designs http://www.firelily.com/opinions/color.html
- Vischeck http://www.vischeck.com/index.php

Most of us take colour vision for granted, but there are still many people who are unable to enjoy its benefits. One in 20 European Caucasian males has a red/green colour vision deficiency, and the internet provides plenty of useful information about this and other types of colour blindness.

Many colour blind people feel that they are discriminated against. Andrew Oakley, who is red/green colour blind, says "we have instructions telling us to 'press the red button', machines which have a green safety light and a red warning light, even colour-coded pills!" He also vents his spleen on light bulbs that change from red to green, which he calls "the work of Satan".

It seems that we need a better understanding of the needs of people with colour vision deficiencies. For example, Diane Wilson from the web design company Firelily Designs offers advice on how to make your web site more user-friendly (handy hint — see how it looks in black-and-white!). Wilson herself is an 'anomalous trichromat'; that is, her red and green cone cells do not function as effectively as they should. If you want to see how your own web site looks to someone with red/green colour blindness, try running it through Vischeck.

Although colour blind people are prevented from doing certain jobs, it's worth noting that they might have certain advantages. Oakley points out that "we look for outlines, not colours, so we don't get easily confused by camouflage", which is why "colour blind people were used in World War II spy planes to spot camouflaged German camps".

Heather Wood

DEVELOPMENT

Nature vs nurture

When reading about neural development in a textbook, chances are that we will find a clear division between activity-dependent processes and those that do not require neural activity. Are there developmental mechanisms that bridge this divide? Although this question has profound implications, this issue has not, so far, been a mainstream area of research. But now Takasu *et al.* have provided a breakthrough in this field by showing that Eph receptors can modulate the function of NMDA (*N*-methyl-D-aspartate) receptor ion channels.

Eph receptors and their ligands, the ephrins, participate in several developmental phenomena, such as segmentation and axon guidance. Previous observations had shown that EphB2 receptors interact with and cluster NMDA receptors at synaptic sites. Takasu *et al.* explored the functional meaning of such an interaction and found that EphB2 potentiates the influx of calcium through NMDA channels in cortical neurons, an effect that depended on phosphorylation of the NMDA receptor. Although Eph receptors are themselves kinases, this NMDA receptor phosphorylation involves a member of the Src family of kinases. As this increase in NMDA receptor function was also accompanied by an increase in gene expression, it is possible that this new signalling pathway participates in the long-term structural remodelling of the synapse. Indeed, two additional papers point in this direction by showing that the absence of EphB2 impairs long-term synaptic plasticity.

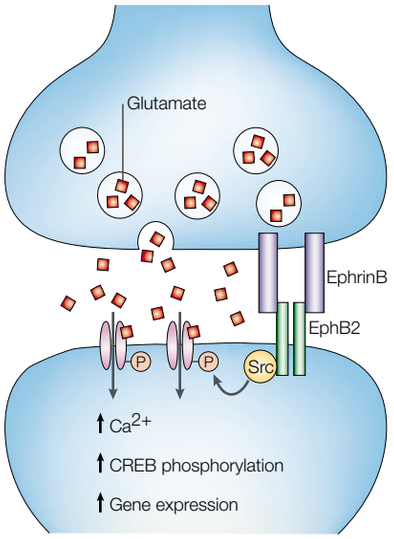
Henderson *et al.* found that mice lacking EphB2 showed a reduction in hippocampal long-term potentiation (LTP) in both the CA1 region and the dentate gyrus. Grunwald *et al.* found a similar reduction in CA1 LTP, particularly during its late phase, and marked impairments of both long-term depression (LTD) and a reversal of LTP known as depotentiation. Moreover, Grunwald *et al.* showed that spatial memory, which depends on hippocampal function, was defective in EphB2 knockout mice.

SENSORY SYSTEMS

Keeping an ear out for modifiers

Although the ability of some mouse genetic backgrounds to modify mutant phenotypes is well known, only a handful of the responsible modifier genes have been found. Now Ikeda *et al.* report a new mouse modifier gene — *Mtap1a* — that rescues the hearing defects of C56BL/6J (B6) tubby (*tub*) mutant mice. Importantly, their findings strongly indicate that Mtap1a interacts with proteins that establish and maintain synapses, and that in the B6 mouse strain, this association is disrupted by *Mtap1a* alleles that carry polymorphisms in functionally important regions of the gene.

The *tub* modifier (*moth1*) locus was mapped to chromosome 2 in 1999, after it was discovered that *tub* mice retain their hearing on some genetic backgrounds, such as on the AKR/J (AKR), CAST/Ei and 129P2/OlaHsd (129P2) mouse strains, while still developing other *tub*-associated phenotypes. So, to



Together, these findings give a significant push to the idea that Eph receptors are crucially involved in synaptic plasticity, although some observations still need to be reconciled. For example, NMDA receptor phosphorylation requires expression of the full-length EphB2 receptor. By contrast, the presence of a version of EphB2 that lacks the intracellular domain is enough to rescue the effect of the knockout on synaptic plasticity. But despite such differences, these three papers have begun to reveal one way in which nature and nurture interact to give rise to the nervous system.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPERS Takasu, M. A. *et al*. Modulation of NMDA receptor-dependent calcium influx and gene expression through EphB receptors. *Science* **295**, 491–495 (2002) | Grunwald, I. C. *et al.* Kinase-independent requirement of EphB2 receptors in hippocampal synaptic plasticity. *Neuron* **32**, 1027–1040 (2001) | Henderson, J. T. *et al*. The receptor tyrosine kinase EphB2 regulates NMDA-dependent synaptic function. *Neuron* **32**, 1041–1056 (2001)
FURTHER READING Wilkinson, D. G. Multiple roles of Eph receptors and ephrins in neural development. *Nature Rev. Neurosci.* **2**, 155–164 (2001) | Gerlai, R. Eph receptors and neural plasticity. *Nature Rev. Neurosci.* **2**, 205–209 (2001)

identify the responsible gene, Ikeda *et al.* finely mapped the *moth1* locus to an interval of 0.17 centimorgans. By screening AKR-derived brain and eye cDNA libraries, Ikeda *et al.* then identified and mapped four additional genes to this region. One of these was *Mtap1a*, which encodes the neuron-specific, microtubule-associated protein 1a. On sequencing these cDNAs from the AKR and B6 strains, only *Mtap1a* contained strain-specific sequence variations — 12 single-nucleotide changes that either altered amino acids or changed the length of an Ala-Pro repeat. The sequencing of CAST/Ei and 129P2 *Mtap1a* alleles also revealed ten amino-acid-changing polymorphisms between these strains and B6. To prove that *Mtap1a* is indeed the modifier at *moth1*, the authors next introduced a 129P2-derived *Mtap1a* transgene into B6 *tub/tub* mice, and almost completely rescued their hearing defects.

So, what is the function of Mtap1a and how does it interact with tubby to protect against hearing loss? It appears that, in B6 mice, Mtap1a function is compromised by polymorphisms in a region of the protein that resembles a guanylate kinase (GUK) binding site. GUK domains are present in a membrane-associated family of proteins that are crucial for the establishment of post-synaptic cytoarchitecture. Ikeda *et al.* found that one member of this family, PSD95, immunoprecipitates with Mtap1a in cerebellar extracts. Moreover, more PSD95 was present in complex with Mtap1a in AKR-derived extracts than in B6 extracts, indicating that sequence polymorphisms in the B6 *Mtap1a* alleles might affect binding between these two proteins. Future studies should establish the physiological significance of this altered binding in neuronal synaptic function and hearing, and should reveal the still unexplained interaction between *Mtap1a* and tubby itself.

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Senior Editor, Nature Reviews Genetics

References and links

ORIGINAL RESEARCH PAPER Ikeda, A. *et al*. Microtubule-associated protein 1A is a modifier of tubby hearing (*moth1*). *Nature Genet.* 4 February (2002). DOI: 10.1038/ng838
FURTHER READING Nadeau, J. Modifier genes in mice and humans. *Nature Rev. Genet*. **2**, 165–174 (2001)

IN BRIEF

NEUROLOGICAL DISORDERS

Anti-*S*-nitrosocysteine antibodies are a predictive marker of demyelination in experimental autoimmune encephalomyelitis: implications for multiple sclerosis.

Boullerne, A. I. *et al. J. Neurosci.* **22**, 123–132 (2002)

The production of nitric oxide and related species such as *S*-nitrosocysteine (SNO-Cys) is associated with multiple sclerosis (MS). The authors had previously shown that MS patients produce antibodies against SNO-Cys. Here, they build on this observation by showing that similar antibodies are present in a rat model of MS, and that the level of antibodies peaks before the onset of clinical signs. Importantly, they found that antibody levels were also elevated in MS patients at times of relapse, but were normal during remission. So, anti-SNO-Cys antibodies might be markers for disease activity in MS.

PAIN

Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model.

Bolay, H. *et al. Nature Med.* **8**, 136–142 (2002)

In people with migraine, headaches are sometimes preceded by a visual aura. Cortical spreading depression, a band of slowly propagating neuronal depolarization that is followed by a long-lasting suppression of neural activity, had been postulated as the cause of the aura. What is the link between the aura and the headache? Here, Bolay *et al.* show that spreading depression activates branches of the trigeminal nerves that innervate the meninges, leading to vasodilation and inflammation. These data establish a direct link between the aura and the headache.

IMAGING

Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain.

Fischl, B. *et al*. *Neuron* **33**, 341–355 (2002)

The authors have developed a method for assigning an anatomical label to each voxel in an MRI sample automatically. Their approach is based on probabilistic information that is estimated from a manually labelled training set. The method can tolerate anatomical variability, is as accurate as manual labelling, and can detect relatively subtle changes in the volume of brain structures. This technique can be applied on a large scale, and the concomitant morphometric information might facilitate the characterization of anatomical changes that accompany different neurological disorders.