HIGHLIGHTS

VISUAL SYSTEM

More than meets the eye

Most of us have known since our schooldays that the mammalian retina contains just two types of photoreceptor cell — rods and cones. Also, despite occasional suggestions to the contrary (such as the controversial claim that illumination of the skin behind the knee can influence the human circadian clock), it is generally accepted that entrainment of mammalian circadian rhythms to the light/dark cycle requires retinal sensory input. It is somewhat surprising, then, to discover that mice lacking both rods and cones retain a strict circadian rhythm. As Lucas *et al*. have now shown in a study published in *Nature Neuroscience*, these mice also retain another non-image-forming response to light, namely the pupillary light reflex (PLR).

Lucas *et al*. generated mice containing the retinal degeneration (*rd*) mutation, which abolishes rod cell phototransduction and ultimately leads to total rod degeneration, and a diphtheria-toxin-based transgene (*cl*), which ablates cone cells. They measured the PLR in response to a monochromatic light stimulus across a range of wavelengths (420–625 nm) and showed that in *rd/rd cl* mice, the PLR response peaked at a wavelength of 479 nm. This observation, combined with the shape of the action spectrum curve, implied that the photopigment mediating the response was of the opsin:vitamin A class, and the authors designated this molecule OP^{479}. Importantly, the action spectrum did not correlate with the absorption characteristics of any known photoreceptors, ruling out the possibility that the PLR was being mediated by rods or cones that had somehow survived ablation.

It is known that fish and amphibians possess retinal photopigments other than those found in rods and cones, and this new study provides the most compelling evidence yet that such molecules also exist in mammals. The next steps will be to elucidate the molecular identity of OP^{479} and to identify the cells in which it functions. It also remains to be seen whether OP^{479} has a significant role in the wild-type eye, or whether it is recruited only in response to rod and cone loss. Just when we thought that it was time to start looking beyond the eyes for new photoreceptors, it seems that the retina is still capable of providing a few surprises.

Heather Wood

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WEB WATCH

Kid's stuff

If you are a parent or a teacher, you have a great excuse to visit the 'Neuroscience for kids' web site. If not, you will just have to hope that nobody looks over your shoulder while you browse.

Run by Eric Chudler of the University of Washington, the site provides a wealth of resources on all parts of the nervous system. The colourful homepage invites you to explore the nervous system, after which you can select a specific subject. For example, if you select sensory systems, you can find a description of the visual pathway, with links to related subjects — the retina and the eye — and to games and activities related to vision. (These are, of course, my favourite bits.)

But there's more. Visitors to the site can send an e-mail to Dr Chudler, and ask a question related to neuroscience. Questions are answered by 'The neuroscientist network', an international group of neuroscientists who answer queries on everything from the number of neurons in the spinal cord to the effects of temperature on the shape of the action potential. There are graded lesson plans and resources, short articles on neuroscience in the news, and a helpful list of neuroscience links. And did you know that a giraffe sleeps for only around two hours each day? Facts like this can be at your fingertips if you follow the link to the treasure trove of brain trivia.

'Neuroscience for kids' is a lot of fun for those of us who never really grew up. But it is also a great way of getting younger students to think about how they think.

Rachel Jones

SLEEP

Out for the count

Around 1 person in 2,000 suffers from narcolepsy — a debilitating disorder that causes extreme sleepiness and is associated with obesity. Recent work has implicated a pair of neuropeptides, the orexins (also known as the hypocretins), in narcolepsy, but their exact involvement has remained unclear. Now, Hara *et al*. have addressed this question by knocking out the hypothalamic neurons that contain orexin.

Previous work had shown that mice lacking the gene for orexins appear to be narcoleptic, and a single human patient has been identified in whom a mutation in this gene led to early-onset narcolepsy. In most sufferers, though, the disease is not monogenic, and the symptoms develop around adolescence. These patients show decreased orexin levels and apparent loss of the orexin-containing neurons of the lateral hypothalamic area.

In an attempt to reproduce this phenotype, Hara *et al*. generated mice carrying a transgene coupled to the *prepro-orexin* promoter so that the gene product, a truncated form of ataxin 3 with 77 polyglutamine repeats that causes apoptosis, would be expressed only in the orexin neurons. When the transgenic mice were born they appeared to be normal, but over the subsequent weeks they showed a gradual loss of orexin neurons, which was almost complete by 15 weeks.

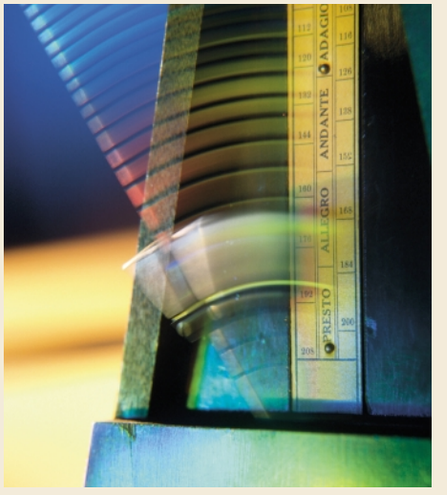
At six weeks of age, when the loss of neurons was between 75% and 90%, the mice began to show symptoms of narcolepsy. When filmed at night (when mice are most active) using infrared video, they showed frequent episodes of 'behavioural arrest' (periods of inactivity) like those seen in *prepro-orexin* knockout mice. The mice also showed increased REM sleep and a highly fragmented sleep/wake pattern during the dark period, and disturbed sleep patterns during the light period.

AUTONOMIC NERVOUS SYSTEM

Rhythms of the periphery

An old colleague of mine used to liken the autonomic nervous system to the suburbs of a city in a condescending way: "why bother going there if there's never anything going on?". Of course, this patronizing view is quite inaccurate; we may not know a lot about what happens in the periphery, but this should actually encourage us to find out more about it. Take, for example, the physiology of the sympathetic neurons that control vasomotor tone. These postganglionic cells show bursts of activity, with a periodicity that is related to the cardiac and respiratory cycles — a coordination that might help to optimize blood supply to every organ. How is this bursting activity controlled? One leading idea is that an oscillatory network in the brainstem entrains the sympathetic neurons, causing them to fire synchronously. In fact, there seem to be not one, but several oscillatory networks, as there is variability in the rhythmic patterns of activity measured in the vascular systems of different organs. And now, a recent paper in *The Journal of Physiology* reports that afferent somatic activity can reset the oscillatory networks and transiently synchronize sympathetic neuron firing, adding an additional complication to this system.

Staras and his colleagues investigated the effect of radial nerve stimulation on the burst firing of the postganglionic



neurons that innervate the caudal ventral artery of the rat tail. They found that, following the stimulus, the activity of sympathetic neurons was first reduced, and subsequently synchronized, in a transient manner. The authors interpreted these findings as evidence that stimulation of the

The transgenic mice also became obese from about 10 or 12 weeks of age onwards. This is despite the fact that they ate less than their wild-type littermates, and probably reflects reduced energy expenditure owing to the reduction in activity levels in the transgenic mice.

The results of this study seem to confirm the importance of the orexin-containing hypothalamic neurons for sleep/wake regulation and energy homeostasis, and may represent a model that will be useful in studying the pathophysiology of narcolepsy and in developing strategies for its treatment. The approach used by Hara *et al*. also has great potential for the investigation of the functions of other groups of neurons, and could be used to generate models of human diseases in which specific neurons degenerate, such as Huntington's disease.

Rachel Jones

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somatic nerve had reset the oscillatory networks, and proposed that this resetting could act to coordinate sympathetic function in response to somatic input. Indeed, this mechanism might have physiological relevance, as Staras *et al*. found that a similar transient synchronization also occurred when they applied a pinch to the rat paw. To discover whether a similar phenomenon is related to the enhanced bursts of sympathetic activity that are associated with stress in humans, we will have to take another trip to suburbia.

Juan Carlos López

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DEVELOPMENT

Organizing the organizer

In the 1920s, Spemann and Mangold showed that the dorsal lip mesoderm of a gastrulating frog embryo could induce the formation of a complete secondary axis. Since then, it has been found that signals from this region, termed Spemann's organizer, are required for neural induction, and many of these signals have been identified. Neural induction requires the inactivation of bone morphogenetic protein (BMP) signalling, and in *Xenopus*, the organizer secretes antagonists such as Chordin, Noggin and Cerberus, which prevent BMPs from binding to their receptors. BMP signalling is also regulated at the transcriptional level, and β-catenin, a component of the Wnt signalling pathway, has been identified as a repressor of the *BMP-4* gene. β-Catenin is already known to act in the blastula to establish dorsoventral polarity and to activate organizer-specific genes. Now a report published in *Developmental Biology* presents evidence that it might function as a neural inducer in its own right.

Wessely *et al*. injected four-cell *Xenopus* embryos with *cerberus-short* (*cer-S*) mRNA, which encodes the carboxy-terminal portion of Cerberus. This inhibits the activity of mesoderm-inducing Nodal-related molecules (Xnrs), and the resulting embryos fail to develop mesoderm and lack Spemann's organizer. Intriguingly, however, they still generated an identifiable anteroposterior neural axis, including a cyclopic eye. The authors then inactivated β-catenin expression in *cer-S*-injected embryos by treating them with ultraviolet light. This blocks a crucial rotation event in the *Xenopus* egg that is required for activation of the Wnt signalling pathway. The ultraviolet treatment prevented neural induction, but the phenotype could be rescued by injecting β-catenin mRNA into the embryos.

The authors re-evaluated the expression of supposedly organizer-specific genes at the blastula stage, and found that the BMP-antagonist-encoding genes *chordin*, *noggin* and *follistatin* were expressed at least 2 hours earlier than was previously thought, even in the *cer-S*-injected embryos. This implies that neural induction might be initiated under the influence of β-catenin at the blastula stage, before the development of the organizer. However, the expression of these genes could not be maintained in the absence of mesoderm, which might explain why the nervous system in *cer-S*-injected embryos showed defects in patterning.

The idea of a 'pre-organizer' in the blastula is not new: a model was previously proposed in which β-catenin activates Xnr expression in the endoderm, leading to mesoderm induction and establishment of the organizer. What is new about this study is that it implies that β-catenin signalling itself can elicit neural induction in the absence of mesoderm. So, to understand how neural induction is initiated, it seems that we will have to turn our attention to events that precede the appearance of the organizer.

Heather Wood

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WEB SITE De Robertis' lab

PRIMATE COGNITION

Rules and regulations

A lot of our behaviour depends on following rules. Some are explicit and concrete: stop your car at a red light. Others, though, are more abstract and can be generalized. For example, we might learn the 'rules' of polite conversation, and then apply them flexibly whenever we meet a new person. Wallis *et al*. have shown that neural activity in the prefrontal cortex of monkeys accurately reflects the coding of abstract rules.

The monkeys were trained to recognize various sensory cues as indicating which of two abstract rules they should apply. For example, if a drop of juice was given when a picture appeared, it indicated that the monkey should release a lever if the next picture it was shown matched the first. A green background, on the other hand, told the monkey to release the lever only if the two pictures didn't match. The activity recorded from individual neurons in the prefrontal cortex during the test sessions showed that many of these neurons — around 40% — had activity levels that depended on which rule was in force. Half of the rule-specific neurons were activated by the match rule, and half by the non-match rule.

It has already been shown that prefrontal neurons can encode concrete rules. These new data reinforce the idea that the prefrontal cortex is also crucial for the ability to implement general principles in varying situations — which is central to intelligent behaviour.

Rachel Jones

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WEB SITE Miller's lab

IN BRIEF

DEVELOPMENT

A developmental compartment regulated by *Lunatic fringe* in the forebrain.

Zeltser, L. M. *et al. Nature Neurosci.* **4**, 683–684 (2001)

In a rare example of compartmentalization in the diencephalon, the authors find that *Lunatic fringe (L-fng)* is expressed throughout the developing avian forebrain, except in a wedge-shaped domain in the middle of the prosencephalon. This domain gradually narrows to form the zona limitans intrathalamica (zli), which separates the ventral and dorsal thalamus. Ectopic expression of *L-fng* can direct cells to segregate out of the zli and can disrupt its formation.

NEUROIMAGING

Nonmonotonic noise tuning of BOLD fMRI signal to natural images in the visual cortex of the anesthetized monkey.

Rainer, G. *et al. Curr. Biol.* **11**, 846–854 (2001)

Our ability to perceive a natural scene decreases monotonically as noise is added. Rainer *et al.* have measured the BOLD activity elicited in the visual cortex of anaesthetized monkeys by visual scenes with and without noise. Natural images elicited more activity than noise patterns, but intermediate levels of noise produced a V-shaped tuning curve of activity. This might reflect an interaction between the small number of neurons activated at high rates by natural scenes and the larger number of neurons activated at low rates by noise patterns.

ION CHANNELS

DEG/ENaC ion channels involved in sensory transduction are modulated by cold temperature.

Askwith, C. C. *et al. Proc. Natl Acad. Sci. USA* **98**, 6459–6463 (2001)

The search for a cold-sensitive channel continues. Some cation channels of the DEG/ENaC family, which are expressed in sensory neurons of the skin and tongue, might function as taste or mechanoreceptors. As the perception of taste and touch can change with temperature, Askwith *et al.* report that cold temperatures increase current flow through these channels by slowing desensitization.

CIRCADIAN RHYTHMS

Nonredundant roles of the *mPer1* and *mPer2* genes in the mammalian circadian clock.

Zheng, B. *et al. Cell* **105**, 683–694 (2001)

Differential functions of *mPer1*, *mPer2*, and *mPer3* in the SCN circadian clock.

Bae, K. *et al. Neuron* **30**, 525–536 (2001)

These papers describe the effects of single and double mutations of *mPer1* and *mPer2*. Either mutation disrupts the circadian period, but double-knockout mice are arrythmic. The effects of these mutations on the expression of other clock genes show that the proteins are complementary: mPER1 regulates other proteins post-transcriptionally, whereas mPER2 regulates clock gene expression.

STEM CELLS

The A to C of neuronal maturation

The finding of neuronal stem cells in the adult brain has pointed to new avenues of treatment for neurodegenerative diseases and traumatic brain injury. But realizing the clinical potential of this knowledge will depend on an understanding of the molecular mechanisms that control the fate of stem cells in the central nervous system. How is the switch from immature stem cell to mature neuron achieved? Conti and colleagues have taken an important step towards answering this question by showing that changes in the expression of Shc adaptor proteins occur as cells undergo neuronal differentiation.

Shc proteins couple activated protein tyrosine kinase receptors to downstream signalling pathways, allowing cells to respond to trophic agents such as nerve growth factor. As they report in *Nature Neuroscience*, Conti *et al*. showed that neuronal precursors differ from mature neurons in their expression of two forms of Shc. So, whereas neuronal stem/progenitor cells express ShcA, they were found to be largely devoid of ShcC. Conversely, ShcC was expressed at relatively high levels in the mature brain, unlike ShcA, which was downregulated as development progressed. In fact, ShcC was expressed only in post-mitotic neurons, apparently replacing ShcA, and its level of expression increased with brain maturation.

Conti *et al*. went on to show that ShcA, expressed in cultured neuronal progenitors, and ShcC, expressed in these cells as they differentiated, could be activated equally by the same ligands; but whereas the former supports the proliferation of neuronal precursors, ShcC was found to activate pathways that promote the survival and differentiation of post-mitotic neurons. These data indicate that the switch from ShcA to ShcC drives the transformation of progenitor cells into fully functional neurons. But what causes this shift in expression? Finding the answer to this question could be the next step in our efforts to harness the therapeutic potential of neuronal stem cells.

Rebecca Craven

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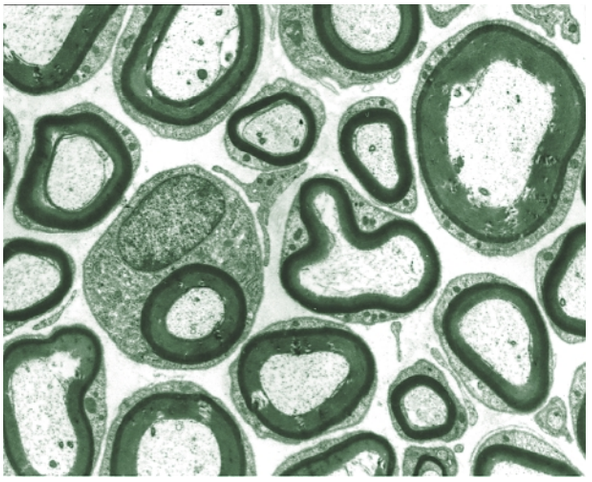
Stem cells (left) and differentiated neurons (right) visualized by immunofluorescence; the expression of ShcA and ShcC is balanced in these cell populations. Courtesy of Elena Cattaneo, University of Milan, Italy.



Electron micrograph of sciatic nerve. Courtesy of J. Milbrandt, Washington University, St Louis, Missouri, USA.

GLIA

Profile of a neuropathy

Many demyelinating diseases have a genetic basis. Although some of these disorders are associated with mutations in myelin proteins such as myelin protein zero and periaxin, this is not always the case. For example, mutations in the transcription factor *EGR2* are found in some patients with inherited peripheral neuropathies. Intriguingly, these neuropathies are transmitted in a dominant manner, but mice heterozygous for an *Egr2* null allele are normal. This observation prompted the suggestion that the mutant *EGR2* gene encodes a dominant-negative mutant protein in people with the disease. But as Nagarajan *et al.* report in *Neuron*, testing this seemingly straightforward hypothesis has led to deeper, unanticipated insights into the mechanisms behind these demyelinating diseases.

The authors first used a conventional approach to test whether mutant Egr2 acted as a dominant-negative inhibitor and could block the expression of a reporter gene. As the results were negative, they wondered whether any dominant-negative activity of the mutant transcription factor would only become manifest if the target genes were in their endogenous loci. However, to explore this idea required the previous identification of Egr2 targets. So, the authors used microarray expression profiling of Schwann cells to identify genes induced by *Egr2* expression, and found that several myelin genes were under the control of this transcription factor. Now, when they tested the effect of mutant Egr2 on the expression of these myelin genes in Schwann cells, Nagarajan *et al.* observed the dominant-negative activity that they had originally tried to find.

So, an inability of the Schwann cells to produce crucial myelin proteins and execute the myelination programme seems to be at the core of the inherited peripheral neuropathies. Importantly, Nagarajan *et al.* obtained evidence that reintroducing the normal *Egr2* gene to cells that express low levels of the protein can lead to the expression of the missing myelin proteins. This finding raises the possibility that the myelination defect might be reversible and opens new avenues for the development of therapeutic measures to treat these debilitating disorders.

Juan Carlos López

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DECISION MAKING

Worth the wait

How do we control our impulses? If the choice is between a small treat now and a large treat later, most of us would choose the large treat, even though we have to wait for it. The inability to overcome the desire for immediate reward in this way is known as impulsive choice; it has been implicated in addiction, attention deficit hyperactivity disorder (ADHD) and some personality disorders, but its cause is unclear.

Rudolf Cardinal and colleagues have investigated the neural substrates of impulsive choice by looking at the preferences of rats for a small, immediate reward or a larger, delayed one. They found that lesions of the nucleus accumbens core reduced the rats' preference for the larger, delayed reward, apparently by making them unable to overcome their impulsive desire for immediate gratification. Unlesioned rats would choose the larger reward on some trials even if it was delayed by up to 60 seconds, but lesioned animals usually chose the smaller reward even if the delay to the larger one was only 10 seconds.

Cardinal *et al*. also tested rats in which either the medial prefrontal cortex (mPFC) or the anterior cingulate cortex (ACC) was lesioned. Both of these areas project to the core of the nucleus accumbens and have been implicated in impulsive behaviour. Surprisingly, neither of these lesions induced impulsive choice in the rats. ACC lesions had no effect on the task, even though such lesions have been implicated in response disinhibition. The authors attribute this apparent contradiction to a dissociation between motor impulsivity and impulsive choice. Rats with mPFC lesions chose the large, delayed reward less frequently than shams at zero delay, but more frequently at the maximum delay. This may reflect an interaction of the mPFC lesion with the specific task used.

It remains to be seen which accumbens afferents are involved in controlling impulsive choice. But these data suggest that the nucleus accumbens may be important in our ability to make rational decisions when faced with this kind of choice, and in its disruption in various disorders. Cardinal *et al*. also suggest that the results may indicate that the nucleus accumbens is the site of action of methylphenidate (Ritalin), which modifies dopamine signalling and can relieve the symptoms of ADHD.

Rachel Jones

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IN THE NEWS

Antidepressant blues

Serotonin re-uptake inhibitors (SRIs) were welcomed as a breakthrough in the treatment of depression. One of the main reasons for their good reception was that SRIs did not cause physical dependence, a clear advantage over their most commonly prescribed predecessors — benzodiazepines. But a couple of recent court rulings in the US and Australia could seriously affect this widespread view and open what might become a large can of worms. In both cases, patients who had been on SRIs killed their relatives and committed suicide after stopping drug intake; the court ordered drug manufacturers to pay damages to the victims' families.

But this might not be all. As reported in *The Guardian* (UK, 11 June), access to the company archives prompted by one of the cases has actually shown that withdrawal symptoms might have been identified in healthy volunteers back in the 1980s, when SRIs were being tested originally. According to the report, "as many as 85% of the volunteers … suffered agitation, abnormal dreams, insomnia and other adverse effects" (*The Guardian*, 11 June). The report goes on to say that a World Health Organization list of drugs, rated by doctors as causing the most problems when people are trying to quit, places SRIs ahead of benzodiazepines.

However, drug manufacturers aren't convinced that there is good evidence for withdrawal effects: "The firms maintain that people who feel worse after stopping the drugs are suffering a recurrence of depression. They are advised to go back to the drugs" (*The Guardian*, 11 June). The debate, of course, is likely to continue for some time, but it is clear that the opportunities for drug discovery in this area are still wide open.

Juan Carlos López

SPATIAL AWARENESS

The rights and wrongs of neglect

Most aspects of sensory or motor processing are controlled by areas of the brain contralateral to the part of the body involved. So, if you want to move your right arm, the command signal comes from the left motor cortex; and somatosensory input from the same arm goes initially to the left somatosensory cortex. But spatial awareness seems to follow this rule only for one side of the brain. New imaging data may shed light on why damage to the right side of the brain, but not the left, can cause neglect of the contralateral side of space.

Coghill *et al*. followed up the observation that lesions of the right posterior parietal cortex, but not the left, can cause tactile as well as spatial neglect on the left of the body. They used PET imaging to study blood flow in the brains of healthy subjects while applying innocuous or painful heat (35 °C or 49 °C, respectively) to the subjects' left or right arms.

Many areas of the brain, such as somatosensory cortex and insular cortex, were activated in response to contralateral stimulation, with the activation increasing as a function of stimulus intensity. Other areas, including the thalamus, cerebellum and anterior cingulate cortex, were activated bilaterally. But the most interesting finding was a network of right-lateralized activation that occurred whether the stimulation was on the left or the right. These results indicate that the representation of the body surface, like those of extrapersonal visual and auditory space, may rely on a network of brain areas found on the right side of the brain.

Exactly where in the brain these areas are is the subject of another debate. For some time it has been known that lesions of the superior temporal cortex in monkeys cause a neglect-like syndrome, but neglect in humans seemed to depend on damage to the posterior parietal lobe. Pinning down the exact area responsible in humans has been complicated by the variable symptoms caused by brain injuries. Karnath *et al*. have used computerized tomography and MRI to carry out a detailed analysis of the locations of lesions in patients with spatial neglect, and show that, as in monkeys, the critical locus seems to be the right superior temporal cortex rather than the posterior parietal region. In monkeys, though, neglect can be caused by lesions on either side. Karnath *et al*. speculate that the development of human language led to the lateralization of spatial awareness to the right superior temporal cortex, as the equivalent area on the left became specialized to process language.

The neural substrate of neglect is clearly complex, and much more work will be needed before we can understand it fully. But papers like these show that at least the field of neglect is not being neglected.

Rachel Jones

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SYNAPTIC PLASTICITY

Don't forget about the presynaptic terminal

What is the locus of expression of long-term potentiation (LTP)? This issue was hotly debated during the past decade. Some researchers argued that this enhancement in synaptic efficacy is due to presynaptic changes — increases in the probability of transmitter release or in the number of release sites. The alternative camp claimed that LTP is expressed postsynaptically and involves changes in the functional properties or the number of receptors. For the most part, however, the field was at a stalemate; most of the evidence obtained in support of both views was indirect or came from the application of quantal analysis, which is based on assumptions that hippocampal synapses might not fulfil. Recently, the scale has tipped in favour of the postsynaptic camp. The discovery of silent synapses and the use of cell biological methods to visualize receptor trafficking directly have made a compelling case for a postsynaptic locus of LTP expression. But a recent paper in *Nature Neuroscience* on the direct visualization of presynaptic changes during LTP indicates that the case is not yet closed.

Zakharenko *et al*. used FM 1-43, a fluorescent dye that is taken up by and released from synapses in an activity-dependent manner, to visualize presynaptic boutons in hippocampal slices. They measured the rate of dye unloading under different conditions and found that it was proportional to release probability. They then explored the effect of LTP on this indicator of presynaptic function, and observed that unloading was faster in potentiated than in control slices. Similarly, if unloading was measured before and after LTP in the same slice, it was faster after potentiation onset. Enhanced presynaptic function was only observed when a strong stimulation protocol was used to induce LTP, supporting the view that LTP is a broad term that encompasses many cellular and molecular processes in both pre- and postsynaptic neurons. So, by moving from classical electrophysiological approaches to the methods of cell biology, the analysis of long-term synaptic plasticity is yielding a more balanced picture of the synaptic components that might underlie learning and memory.

Juan Carlos López

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NEUROTRANSMITTERS

Switching channels

Although GABA (γ-aminobutyric acid) is best known as the main inhibitory neurotransmitter in the adult brain, it can actually excite neurons during embryonic brain development, and in structures such as the hippocampus, neocortex and hypothalamus, its inhibitory properties only emerge after birth. The $GABA_A$ receptor is a chloride channel, and the balance between its excitatory and inhibitory properties depends largely on the Cl^- gradient across the cell membrane. During postnatal development, the switch of GABA-mediated synaptic transmission from excitation to inhibition coincides with the upregulation of expression of the K^+–Cl^- co-transporter KCC2. One consequence of this upregulation is that more Cl^- ions are pumped out of the cell, lowering the resting intracellular Cl^- concentration. But what causes the upregulation of KCC2? A new study by Ganguly *et al.* provides evidence that it might be GABA itself.

The authors isolated neurons from the rat hippocampus just before birth (embryonic day 18), and cultured the cells over a 13-day period. This protocol had previously been shown to accurately replicate the maturation of neurons *in vivo* over the same time period. They then measured the percentage of neurons in which the intracellular Ca^{2+} concentration increased in response to GABA. As the cells matured, they became increasingly unresponsive, indicating that the decrease in the excitatory action of GABA could also be found in culture. Blocking the $GABA_A$ channels with antagonists inhibited this change in responsiveness, and also prevented the switch from GABA-mediated excitation to inhibition. Conversely, the switch was accelerated when $GABA_A$ receptor activation was increased by treating the cells with KCl to induce synaptic GABA release. The authors also observed that GABA regulates the levels of KCC2 mRNA expression, and they suggest a mechanism for this. They propose that depolarizing GABA-mediated potentials activate voltage-dependent calcium channels, setting off a signalling cascade that culminates in the upregulation of KCC2 gene expression. This is further supported by the observation that blocking L-type calcium channels also delayed the switch.

So, Ganguly *et al.* have provided strong evidence that a causal relationship exists between excitatory GABA-mediated transmission and the levels of KCC2. In this way, GABA could indirectly regulate the Cl^- gradient across the cell membrane, leading to a switch in the transmission properties of its own receptor.

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References and links

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LEARNING AND MEMORY

Finding a home for your savings

You're at the pub and the jukebox suddenly starts playing that song from your teenage years. You haven't heard it for ages and your recollection of the lyrics is sketchy at best. But as you listen, the words quickly come back as if they'd never left you; you can remember the whole song so well again that you cannot get it out of your mind for several days. This uncanny ability to relearn information much faster than on the original training is called 'savings'. Despite its importance, however, our understanding of savings is rudimentary. What is the neural basis of savings? Where is it implemented? In a recent paper, Medina *et al.* give some tentative answers to these questions in the context of a cerebellum-dependent form of classical conditioning.

Eyelid conditioning is arguably the best-studied form of motor learning. In this model, a rabbit learns to close the eyelid in response to a tone that is repeatedly paired with periorbital electrical stimulation. The neural circuits involved in eyelid conditioning are well understood, and it has been proposed that changes in synaptic strength in the cerebellar cortex and in the deep cerebellar nuclei might be cellular correlates of this form of learning. Armed with this knowledge, Medina *et al.* built a computer model that could 'learn' and 'extinguish' the eyeblink response, and asked whether it could also show savings during relearning. Indeed, the model relearned faster and they found that residual plasticity in the nucleus interpositus could account for the savings. The authors then predicted that the induction of plasticity in the nucleus interpositus of the actual rabbit should parallel eyelid conditioning, that plasticity should persist after the behavioural response had been extinguished, and that the rate of relearning should correlate

with the amount of residual plasticity in individual rabbits. Indeed, subsequent experiments allowed them to obtain empirical evidence in support of these predictions.

The profound anatomical knowledge of eyelid conditioning was crucial for the success of this study. It would now be interesting to perform similar experiments in other tasks for which the anatomical substrates are well-understood — fear conditioning, for example — to determine whether the mechanism found by Medina *et al.* is also at work in other systems.

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