HIGHLIGHTS

NEUROPHYSIOLOGY

Cause for excitation

Levels of extracellular dopamine are regulated by the dopamine transporter (DAT), a Na^+/Cl^--dependent transporter that is found on dopamine neurons. But there is evidence that DAT might have another role, as described by Ingram *et al.* in *Nature Neuroscience*. They find that activation of DAT triggers a current that increases the excitability of midbrain dopamine neurons.

Interest in DAT is high because both amphetamine and cocaine increase extracellular dopamine by interfering with DAT's ability to clear dopamine from the intercellular space. This increase in dopamine is thought to contribute to the rewarding effects of these drugs. Cocaine is an inhibitor of DAT, whereas amphetamine is a DAT substrate that competes with dopamine for occupancy of the transporter. Previous studies showed that amphetamine could have an excitatory effect on dopamine neurons that is independent of dopamine receptor activation; the new work looked for a potential mechanism of this action.

Ingram and colleagues investigated the effects of low concentrations of dopamine or amphetamine on cultured rat midbrain dopamine neurons. Normally, extracellular dopamine acts on D2 autoreceptors to inhibit the firing of dopamine neurons. But both dopamine and amphetamine increased the firing rate of the neurons in the presence of inhibitors of dopamine D1, D2 or adrenergic receptors. This excitation was caused by a DAT-mediated inward chloride current.

When they analysed the kinetics of the DAT-mediated currents, the authors found that the dopamine affinity of the currents was tenfold higher than the affinity for dopamine uptake by DAT. In other words, the DAT currents were uncoupled from the uptake of dopamine and did not result simply from ionic movements associated with dopamine transport.

An important question is whether this conductance is physiologically relevant. Dopamine neurons *in vivo* are tonically active with complex firing patterns, and regulation of these patterns is likely to be important for the modulation of dopamine release. Neurons contain tightly regulated concentrations of chloride ions, and the chloride equilibrium potential is generally close to the resting potential. This means that small changes in membrane potential that result from the DAT chloride current could have important effects on neuronal excitability and dopamine release.

The DAT-mediated conductance might be important in the somatodendritic release of dopamine from midbrain neurons. According to the authors, depolarization of the neurons by this mechanism provides an alternative to a previous theory — that somatodendritic release results from the reversal of DAT transport and subsequent dopamine efflux. Much more work will be needed to establish the physiological functions of DAT-mediated conductances *in vivo*.

Rachel Jones

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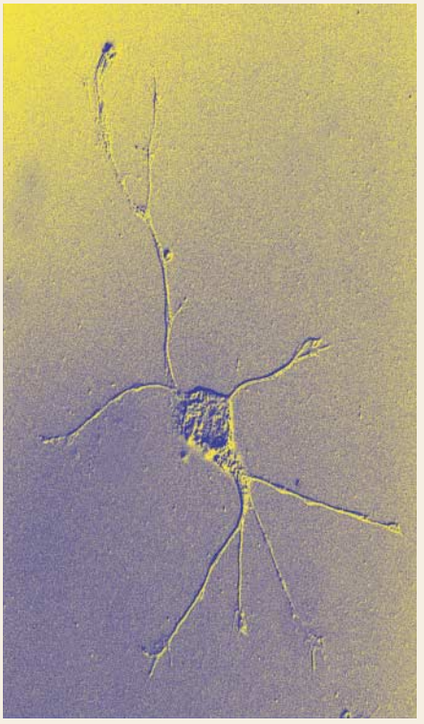
WEB SITES

Encyclopedia of Life Sciences: http://www.els.net/dopamine

DEVELOPMENT

A new direction for frizzled



Wnt signalling is involved in numerous aspects of neural development, but it has not previously been implicated in axonal outgrowth. Now, Wang *et al.* have filled this gap in its functional repertoire, by showing that the Wnt receptor frizzled 3 (Fz3) is required for the development of major axonal tracts in the mammalian forebrain.

The authors knocked out the *fz3* gene in mice, and found that four axonal tracts were missing — the thalamocortical, corticothalamic and nigrostriatal tracts, and the anterior commissure, which connects the left and right hemispheres of the brain. The corpus callosum was also absent in some cases. The mutation did not seem to cause any primary defects in the proliferation or survival of neuronal precursors, so it is unlikely that the phenotype resulted simply from the loss of neurons that give rise to the axonal tracts.

Wang *et al.* asked whether the *fz3* mutation affects the intrinsic ability of forebrain neuronal precursors to develop axons. They found that, when these cells were isolated in culture, they readily adopted a typical neuronal morphology, with a full complement of axons and dendrites. So, it is more likely that the mutation affects the neuron's ability to interpret signals from its environment. The authors suggest that Fz3 might protect the neuron against signals that inhibit axonal outgrowth.

Another clue to the function of Fz3 came from studies in *Drosophila*. The *Drosophila* Fz protein regulates cell polarity, and in the wing epithelium, it determines the point on the cell surface from which a hair will grow. Therefore, another possibility is that Fz3 could determine the direction of neurite outgrowth, perhaps by regulating the neuronal cytoskeleton. This hypothesis could be tested by examining the subcellular localization of Fz3.

These findings point to a new direction for studying Wnt signalling in neural development. It will be interesting to delve into the mechanisms by which Fz3 controls axonal outgrowth, and to find out whether any other members of the frizzled family have similar functions in other regions of the nervous system.

Heather Wood

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ADDICTION

The ups and downs of nicotine

Nicotine is often thought of as a rewarding stimulus. But it also has aversive properties, and these different motivational effects seem to be mediated by circuits that include the ventral tegmental area (VTA). Laviolette *et al.* now take a step towards unravelling these circuits, by showing that lesions of the tegmental pedunculopontine nucleus (TPP) can cause a switch in the motivational effects of nicotine infusions into the VTA, from rewarding to aversive.

The TPP receives inputs — thought to be inhibitory and mediated by GABA (γ-amino-butyric acid) — from the VTA, and sends cholinergic projections back to the VTA. Previous studies have shown that the TPP is important for the rewarding effects of several drugs. In the new study, Laviolette *et al.* infused nicotine directly into the VTA of rats, where it produced a rewarding effect, measured by conditioned place preference. But when the TPP was lesioned bilaterally, the rewarding effect was blocked, and instead the rats showed a conditioned aversion for sites associated with nicotine infusion. TPP lesions did not block the induction of conditioned taste aversion by systemic nicotine administration — another measure of the aversive effects of nicotine.

So, it appears that the TPP is crucial for the rewarding effects of nicotine in the VTA, and that removal of the TPP reveals an aversive effect that is presumably mediated by a different circuit. The authors suggest that, whereas the aversive effects of nicotine are mediated by an ascending dopaminergic system, its rewarding effects are mediated by a non-dopaminergic pathway that includes the TPP.

Rachel Jones

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ION CHANNELS

S4 opens another cork

HCN channels are gated by hyperpolarization and cyclic nucleotides. As changes in membrane potential activate them, HCN channels must have a voltage sensor. In other voltage-activated channels, the fourth transmembrane domain of the protein — the S4 segment — fulfils this role. So, when exposed to voltage changes, the charged amino acids of S4 cause it to rotate and move outwards like a corkscrew, leading to channel opening. As HCN channels also have an S4 segment, this domain might also be the voltage sensor. However, the 'corkscrew' model accounts for the behaviour of depolarization-activated channels. How does the S4 segment of HCN channels behave in response to hyperpolarization? Data from Männikkö *et al.* indicate that S4 is indeed the voltage sensor of HCN channels, but that, in this case, the inward movement of S4 leads to channel opening.

To explore whether S4 of HCN channels moves in response to voltage changes, the authors used the cysteine-accessibility method: they mutated the different residues of S4 to cysteines, and measured the accessibility of these cysteines to thiol reagents while the channel was open or closed. Using this method, it is possible to chart the positions of the residues with respect to the membrane and the solvent, and to outline their movement during channel activation. Männikkö *et al.* found that, similar to potassium channels (which are gated by depolarization), S4 moved in response to changes in membrane potential. But in this case, it was the inward movement of S4 in response to hyperpolarization that caused the channel to open.

So, the voltage-sensing mechanism is conserved in channels that are activated by voltage changes in opposite directions. As the actual channel gate seems to be near the intracellular side of the pore in both types of channel, we need to discover how voltage sensing is coupled to channel gating before we can understand how analogous movements of S4 lead to opposite effects on opening. Grasping how this coupling works is one of the great challenges in the field of ion channel function.

Juan Carlos López

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NEUROLOGICAL DISORDERS

Lesions with a jagged edge

What is good for the embryo is not necessarily good for the adult, as a new report in *Nature Medicine* illustrates. In this paper, John *et al.* show that a signalling pathway that controls oligodendrocyte maturation in the embryo might contribute to the pathogenesis of multiple sclerosis (MS) if it is reactivated in the adult.

MS is an inflammatory disease that causes progressive demyelination in the central nervous system. This initially causes a deficit in axonal conduction, and unless remyelination occurs, the axons eventually degenerate because they lack the trophic support that myelin provides. In the early stages of the disease, the lesions are repaired quite efficiently, but the capacity for remyelination declines with time. However, even the most advanced lesions contain oligodendrocyte precursors that should be able to repair the damage, so why do they lose this ability in the later stages of MS?

The authors considered what other factors at the lesion site might be interfering with remyelination. The cytokine TGF-β1 (transforming growth factor-β1) is known to be present, and reactive astrocytes have also been implicated in the pathogenesis of MS. To examine how these components might interact to prevent remyelination, John *et al.* used microarray analysis to find out how TGF-β1 affects the gene-expression profile of astrocytes *in vitro*.

One factor that was found to be upregulated in the presence of TGF-β1 was a protein called jagged 1. During normal development, jagged 1 acts as a ligand for Notch, which is expressed on the surface of immature oligodendrocytes. Binding of jagged 1 to Notch activates the expression of the basic helix–loop–helix transcription factor Hes5 in the oligodendrocyte precursors, and this prevents them from differentiating too early. The authors found that jagged 1 was expressed in active demyelinating lesions, but not in lesions in which remyelination was successful. This indicates that thejagged–Notch–Hes5 pathway is likely to be one of the factors that prevent the oligodendrocyte precursors in MS lesions from acquiring a mature myelinating phenotype.

Although TGF-β1 is deleterious in terms of remyelination, blocking its activity altogether is not a viable option, because it also protects against inflammation. These new findings raise the possibility of intervention further downstream — for example, by interfering with Notch signalling — and this could lead to the development of new therapeutic strategies for the treatment of MS.

Heather Wood

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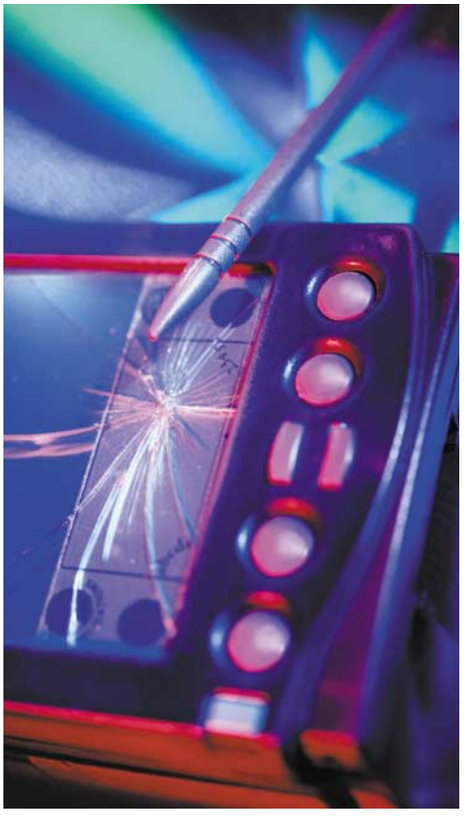

WEB WATCH

How to visualize something really small

- Synapse Web
  http://synapses.bu.edu/

If you want to know how, you must pay a visit to Synapse Web, a fabulous web site of the Laboratory of Synapse Structure and Function at Boston University. Here, you will find information on the ultrastructure of the nervous system at all levels, with a particular emphasis on synapses.

Synapse Web includes introductory information on brain anatomy, and on the structure of dendrites, axons, astrocytes and synapses. It also includes brief accounts of some of the classical microscopic methods that are commonly used in structural studies. This section, which is illustrated by some simple animations, is poised to grow to include descriptions of more recently developed anatomical techniques.

The site also hosts an extraordinary Atlas of Ultrastructural Neurocytology by Josef Spacek, a reference resource in which you can find ultrastructural descriptions not only of neurons and glia, but also of blood vessels, the meninges and the diseased brain.

Last, for those researchers whose work draws heavily on neuroanatomical methods, Synapse Web hosts a collection of software tools to address the challenge of "how to visualize something really small". These tools are intended for the analysis and reconstruction of three-dimensional images from serial sections, and the web-site creators have shown, with some elegant examples, how such tools can be put to good use.

Synapse Web is supported by the Human Brain Project as part of their efforts to stimulate the development of neuroscience databases. This web site is a great initiative that will undoubtedly continue to mature, but it already deserves recognition and appreciation by the community.

Juan Carlos López

VISUAL SYSTEM

Cortical colour contrast

The earliest cortical area in the visual processing pathways is area V1. Although the properties of neurons in V1 have been studied extensively, there is still much controversy over how they contribute to the processing of visual stimuli; for example, do different neurons in V1 respond specifically to different parts of the stimulus — its colour, form or direction of motion, for example — or do they 'multiplex', responding to all of these aspects at the same time? A study published by Conway, Hubel and Livingstone in *Cerebral Cortex* lends weight to the former view.

The authors investigated the neural basis of colour contrast, which causes red, for example, to look more red if it is surrounded by or preceded by its opponent colour, green. They recorded from neurons in area V1 in macaque monkeys, whose colour vision is very similar to that of humans. The monkeys were shown coloured spots that were designed to selectively alter the level of stimulation of one set of cones (for example, the green spot used increased the excitation of M cones, but did not change the activity of S or L cones, when compared with the grey background). Conway *et al*. used these stimuli to map and characterize the receptive fields of the V1 neurons, and found that a subset of these cells could be classified as 'colour' cells, because they showed an 'on' (excitation) response to one colour (for example, red) and an 'off' response to the opponent colour (in this case, green).

These colour cells showed no direction selectivity and only very coarse orientation preference, which supports the idea that colour, form and motion are processed separately in V1, at least to some extent. But many of them showed another interesting property: they had double-opponent receptive fields. This means that the centre and the surround of the receptive field both responded with opposite signs to opponent colours, but that they also responded in the opposite direction to each other. For example, a cell with a red-on, green-off centre would respond with increased excitation to a red spot in the centre of the receptive field or to a green spot in the surround, and with inhibition to a green spot in the centre or a red spot in the surround.

When the authors used pairs of spots of opposing colours — one in the centre of a receptive field and one towards the edge — they found that the cells summed their responses linearly. So, the cell described above would respond more strongly to a red spot in the centre and a green spot in the surround than to either spot alone. This could be the neural basis of spatial colour contrast, because it would lead to a stronger 'red' response when the red stimulus was adjacent to a green patch.

What about temporal colour contrast? When the monkeys viewed pairs of spots separated in time rather than in space, the cells showed temporal opponency: a cell that was excited by the onset of a red spot, for instance, would be suppressed by its offset, whereas a green spot that caused suppression at its onset would lead to the cell being excited at its offset. These temporal responses also summed linearly, so that, if our example cell was suppressed by a green spot and then excited by its offset, the total response to a subsequent red spot — which also excites the cell — was greater than if the red spot had not been preceded by the green spot. Again, this property could contribute to the psychophysical phenomenon of temporal colour contrast.

This kind of quantitative study allows us to compare neuronal properties with perceptual experience, as measured by psychophysics. Although it is still possible that cells in V1 'multiplex' different features of the visual world, these data support the view that only a subset of V1 neurons contributes to colour vision.

Rachel Jones

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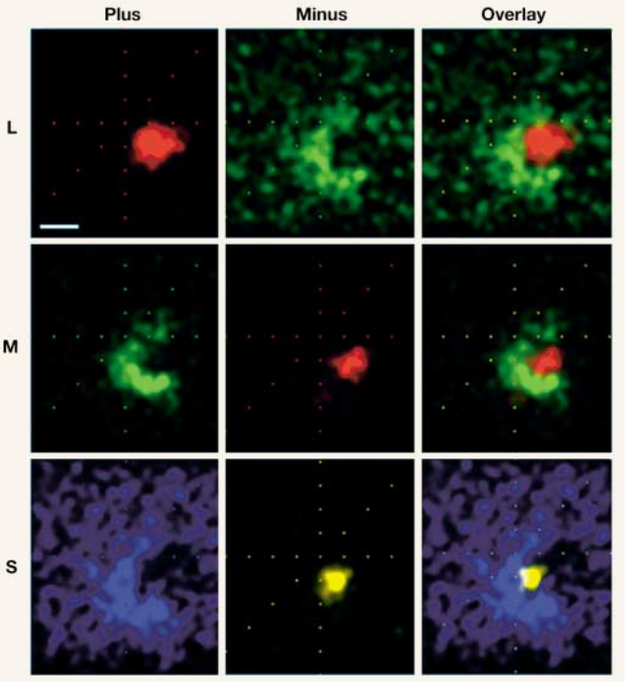

Receptive field map of a double-opponent cell in monkey V1. L, M and S are the cone types; responses are shown to a stimulus that increases (left column) or decreases (middle column) the L, M or S activity; an overlay (right column) illustrates the double opponency. © 2001 Society for Neuroscience (courtesy of B. Conway, Harvard Medical School).

VISUAL SYSTEM

Putting the visual cycle in the shade

In animals with colour vision, the retina contains at least two types of photoreceptor cell. Rod cells function optimally at low light intensities, whereas daylight vision is mediated predominantly by cone cells. Light causes visual pigments in the photoreceptors to undergo a chemical reaction, and for the cell to maintain its photosensitivity, the pigment must be recycled continually. An enzymatic pathway called the visual cycle was thought to be responsible for this process, but it has become clear that this pathway is too slow to maintain photosensitivity during constant exposure to light. Now, however, Mata *et al.* have identified a new, faster regeneration mechanism that seems to be exclusive to cone pigments.

The photosensitive component of the visual pigment is the vitamin A derivative retinaldehyde. When a photoreceptor is exposed to light, the 11-*cis* form of retinaldehyde is isomerized to the all-*trans* form, and to restore the photoreceptor to its resting state, it must be converted back to the 11-*cis* form. Mata *et al.* analysed retinas from the chicken and the ground squirrel, both of which contain a high proportion of cones. They found three previously unidentified enzymatic activities — an all-*trans*-retinol isomerase, an 11-*cis*-retinyl ester synthase and an 11-*cis*-retinol dehydrogenase — which form a pathway that catalyses the conversion of all-*trans*-retinaldehyde to the 11-*cis* form. Interestingly, the level of enzymatic activity was proportional to the percentage of cones in the retina, indicating that this pathway might be important for cone pigment regeneration. The rate of pigment regeneration through the new pathway was 20 times faster than that of the classical visual cycle, and the authors calculate that this should be sufficient to sustain vision in all but the brightest sunlight.

It seems surprising that this alternative pathway has gone unrecognized for so long, but this might be explained by the fact that previous studies on visual pigment regeneration have focused on rod-dominant retinas, such as those of the mouse or the cow. As this pathway has already been identified in two quite distantly related species, it is expected to be a common mechanism for all animals that use cones for daylight vision.

Heather Wood

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IN BRIEF

LANGUAGE

Selective priming of syntactic processing by event-related transcranial magnetic stimulation of Broca's area.

Sakai, K. L. *et al. Neuron* **35**, 1177–1182 (2002)

Lesions of Broca's area cause aphasia, but it is not clear whether this effect is related to a syntactic or a semantic deficit. Sakai *et al.* used transcranial magnetic stimulation (TMS) to interfere transiently with the activity of Broca's area while subjects were required to judge whether a series of sentences were semantically or syntactically normal. They found that the effect of TMS was limited to syntactic decisions, highlighting the role of Broca's area in syntactic processing.

NEUROLOGICAL DISORDERS

Intracellular ataxin1 inclusions contain both fast- and slow-exchanging components.

Stenoien, D. L. *et al. Nature Cell Biol.* 30 September 2002 (doi:10.1038/ncb859)

Polyglutamine protein aggregates are dynamic.

Kim, S. *et al. Nature Cell Biol.* 30 September 2002 (doi:10.1038/ncb863)

These two papers highlight the dynamic nature of polyglutamine protein aggregates. In the first article, the authors used fluorescence recovery after photobleaching to identify two types of ataxin 1 inclusions — aggregates in which ataxin 1 is rapidly exchanged with the soluble pool, and aggregates in which such an exchange is slow. As slow-exchanging aggregates contain high levels of ubiquitin but not of proteasomes, the authors suggest that proteasomes might fail to recognize the ubiquitinated substrates in this type of aggregate. In the second paper, the authors used the same technique and a related method (fluorescence loss after photobleaching) to reveal that the association of the chaperone Hsp70 with huntingtin aggregates is not irreversible, as was previously thought, but transient. This finding challenges the assumption that polyglutamine disorders affect neuronal function by sequestering essential components of the cellular machinery. The dynamic nature of polyglutamine protein aggregates highlights the potential of therapeutic interventions that aim to promote their dissolution.

NEUROLOGICAL DISORDERS

A *Drosophila* fragile X protein interacts with components of RNAi and ribosomal proteins.

Ishizuka, A. *et al. Genes Dev.* **16**, 2497–2508 (2002)

Fragile X syndrome is a form of mental retardation that is caused by alterations in the function of the FMR1 protein. Studying the *Drosophila* homologue of FMR1 (Fmr1), the authors found that a complex of proteins that mediate RNA interference (RNAi) in the fly can interact directly with the Fmr1 protein. RNAi is an important gene-silencing mechanism that has been described mainly in *Drosophila* and plants. These findings raise the possibility that a regulatory mechanism of this type might also be related to human disease.

CELL BIOLOGY OF THE NEURON

Losing touch with sodium channels

Cold sores — those annoying blisters that occasionally appear around the mouth, causing tingling, pain and loss of touch sensation — are caused by the herpes simplex virus-1 (HSV-1). We know that this neurotropic virus infects sensory neurons and reduces their excitability, but the molecular mechanism of its action remains poorly understood. Reporting in *The Journal of Cell Biology*, Storey *et al.* show that HSV-1 infection reduces the membrane expression of sodium channels in primary sensory neurons, uncovering a new way in which neuronal excitability can be regulated.

Using voltage-clamp techniques, the authors found that the amplitude of sodium currents in dorsal root ganglion cells was markedly reduced 24 hours after HSV-1 infection. By staining infected neurons with an antibody against the sodium channels, they obtained evidence for a decrease in the amount of channel protein in the plasma membrane. Moreover, blocking membrane internalization, which does not affect viral entry, prevented the reduction of sodium currents.

How does the virus exerts its effect? As a first step to address this issue, Storey *et al.* set out to determine the relevance of the different stages of viral infection to the change in current amplitude. They found that blocking viral envelopment did not stop the loss of sodium currents in the infected neurons. By contrast, blocking the synthesis of viral DNA — a manipulation that eliminates the expression of 'late' but not 'early' viral proteins — prevented the

NEUROTECHNIQUE

A bright idea

The intrinsic brightness of green fluorescent protein (GFP) and the fact that it can be used to make fusion-protein constructs make it an invaluable tool for studying biological processes *in vivo*. However, its value would be significantly greater if it could be used to selectively mark proteins through photoactivation — a goal that has now been achieved thanks to work published by Patterson and Lippincott-Schwartz in *Science*. These authors had the bright idea of making a GFP that remains 'off' until it's switched 'on'.

GFP normally exist in two forms — a 'neutral' and an 'anionic' form, which produce major and minor absorbance peaks, respectively. Intense illumination with ~400-nm light converts GFP mainly to the anionic form, which results in an increase in minor peak absorbance, as well as a subsequent threefold increase in fluorescence after excitation at 488 nm.

Patterson and Lippincott-Schwartz therefore decided to search for a GFP variant with a reduced minor absorbance peak. They hoped that if they could find such a variant, it would mean that photoconversion with ~400-nm light would produce a larger increase in minor peak absorbance, and therefore a more marked increase in fluorescence after 488-nm excitation.

Because a previously reported GFP mutation at threonine 203 resulted in reduced absorbance at 488 nm without affecting the major absorbance peak, the authors studied various substitutions at this position and found what they were looking for in the form of a histidine substitution. They called this stable GFP variant photoactivatable GFP (PA-GFP), because they found that it had virtually undetectable absorbance at the minor peak and that irradiation with ~400-nm light resulted in a large increase in minor peak absorbance. They also found that 488-nm excitation of photoconverted PA-GFP produced an ~100-fold increase in fluorescence.

So, how useful is PA-GFP for studies in living cells? When the authors studied cells expressing PA-GFP, they found that, in contrast to cells expressing wild-type GFP, 488-nm excitation produced very little fluorescence before photoconversion. Furthermore, after photoconversion with ~400-nm light, they saw that 488-nm excitation produced a more than 60-fold increase in fluorescence for PA-GFP-expressing cells, compared with only an ~2.6-fold increase for wild-type-GFP-expressing cells.

Patterson and Lippincott-Schwartz concluded their report by highlighting some of the biological applications of PA-GFP. They showed that it can be used both as a free protein to study protein dynamics (they looked at protein diffusion across the nuclear envelope) and as a chimeric construct to study membrane dynamics (they used it to monitor interlysosomal membrane exchange). Both of these approahes will find many applications in the study of cellular processes in neurons. All in all, the stability and optical contrast of PA-GFP, combined with the fact that signals can be obtained from it rapidly and specifically, mean that searching for PA-GFP was a very bright idea indeed.

Rachel Smallridge,
Associate Editor,
Nature Reviews Molecular Cell Biology

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WEB SITES

Jennifer Lippincott-Schwartz's laboratory: http://dir2.nichd.nih.gov/nichd/cbmb/sob/Jennifer_Lippincott_Schwartz.html

Encyclopedia of Life Sciences: http://www.els.net green fluorescent protein

decrease in current amplitude. The authors further established that the late viral protein ICP34.5 is crucial for the effect of HSV-1 on sodium currents, as infection with viruses that lack such a protein did not result in sodium channel loss.

In addition to identifying a mechanism to account for the decrease in neuronal excitability that accompanies HSV-1 infections, the data of Storey *et al.* point to a new way to regulate the availability of sodium channels at the plasma membrane. What intracellular pathways does this process engage? Do neurons use this mechanism under physiological conditions? HSV-1 and, in particular, ICP34.5 will be useful tools to answer these questions.

Juan Carlos López

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Image courtesy of Tom Wilson.

LEARNING AND MEMORY

Action replay

The fact that we are able to recall previous events in detail, even those from the distant past, indicates that we have a robust neural system for the acquisition and storage of memories. But despite this impressive storage capacity, in the minutes to days after an event, our memory of the experience is prone to disruption. Hoffman and McNaughton argue that this period of lability reflects the way in which new memories are converted into a long-lasting form. Reporting in *Science*, they provide evidence that memory consolidation involves the reactivation of distributed components of 'memory traces' during periods of behavioural inactivity that follow an event.

According to the 'trace-reactivation theory' of memory consolidation, in 'offline' periods after an event — for example, during quiet waking or sleep — neurons in higher-level cortical regions are thought to activate cells in lower-level regions that were also active during the experience. Repeated co-activations of lower-level ensembles result in the formation of connections that are necessary to encode the memory trace. Previous studies have shown that patterns of cortical activity that accompany an experience can be triggered spontaneously during subsequent periods of rest. Hoffman and McNaughton set out to test a second prediction of the theory — that distributed components of the reactivated memory trace should appear concurrently within relevant cortical sites.

The authors implanted a 12-by-12 lattice of electrodes into each of four areas of the primate neocortex — posterior parietal cortex (PP), motor cortex (M), somatosensory cortex (SS) and dorsal prefrontal cortex (PFC). They recorded simultaneously from multiple individual neurons during an initial period of rest (rest 1), a sequential reaching behaviour and a second period of rest (rest 2). Cell-pair firing-rate correlations were then calculated for each epoch. The authors found that, for PP–PP, M–M, SS–SS, PP–M, PP–SS and M–SS cell pairs, firing correlations during the task were more similar to those of rest 2 than to those of rest 1. This indicates that neurons that were co-activated in these regions during the task tended to be activated together afterwards. No such pattern was seen for cell pairs that included neurons of the PFC. Hoffman and McNaughton went on to show that the 'temporal bias' of cell-pair interactions during the task was preserved in rest 2 in the M and SS. So, if one cell tended to fire after another during the task period, then this firing sequence tended to recur in rest 2. This preservation of temporal bias was not observed for PFC neurons.

These data lend support to the proposal that memory-trace reactivation occurs in a coordinated, distributed manner across the neocortex. Interestingly, no evidence was found of trace reactivation in the PFC, which has been implicated in memory retrieval in humans. Further studies will be needed to elucidate the mechanisms that underlie memory-trace reactivation, and to establish whether or not the PFC has a part to play in this process.

Rebecca Craven

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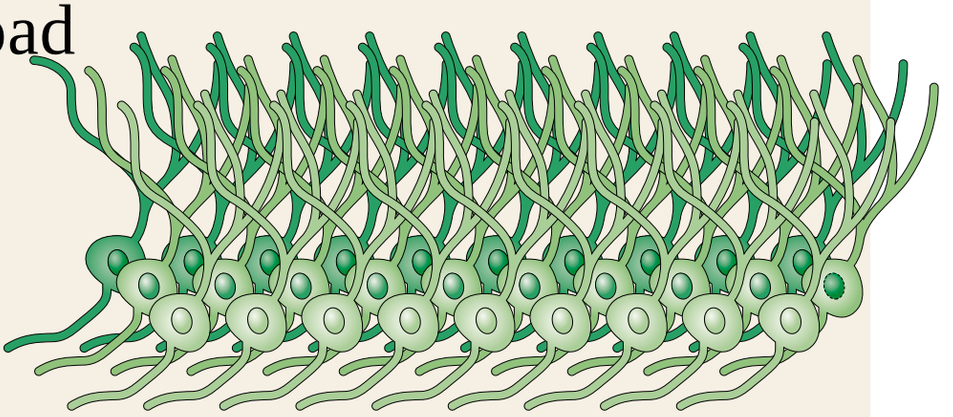
WEB SITES

Encyclopedia of Life Sciences: http://www.els.net
amnesia | learning and memory

NEUROGENESIS

Take the low road



Until recently, a commonly held view in neuroscience was that neurogenesis does not occur in the adult brain. However, this idea was overturned by the discovery that new neurons are generated in the subventricular zone (SVZ). These neurons have been shown to colonize several structures, including the olfactory bulb and the hippocampus, and the list of possible destinations continues to grow, as a report in the *Proceedings of the National Academy of Sciences* illustrates.

Bernier *et al.* used 5-bromodeoxyuridine (BrdU), a thymidine analogue that is incorporated into the DNA of dividing cells, to identify sites of neurogenesis in adult monkey brains. They detected BrdU-labelled cells in the amygdala and piriform cortex, and they used immunostaining techniques to confirm that these cells were neurons. In addition, they identified a stream of BrdU-labelled cells that stretched from the temporal horn of the lateral ventricle (tLV) down to the dorsal amygdala. By labelling the SVZ with the lipophilic dye DiI, and tracking cell migration from the tLV, the authors provided further evidence for the existence of this migratory stream, which they termed the temporal stream.

The amygdala is probably best known for its role in mediating the fear response, but it also acts as a relay centre for olfactory information, as does the piriform cortex. Therefore, Bernier *et al.* speculate that new neurons might be generated in these regions to complement the turnover of olfactory bulb neurons that project to them. Of course, the real test will be to show that the new neurons integrate functionally into the neuronal circuitry, and the next step will be to find out whether this is the case.

Heather Wood

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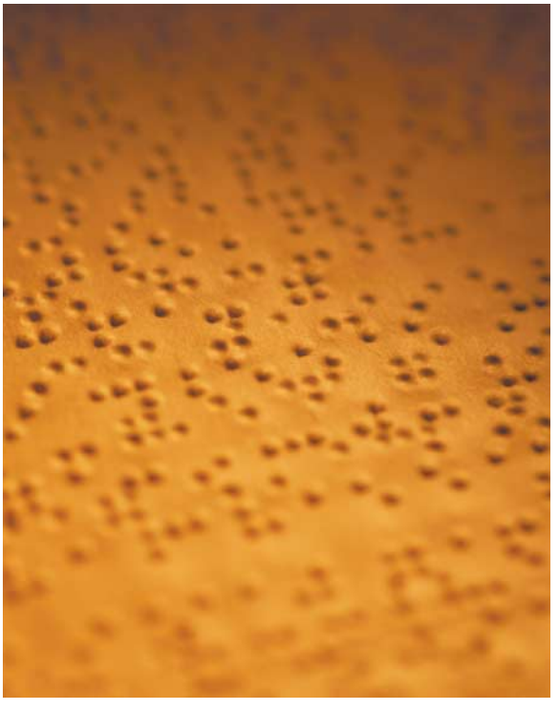
DECISION MAKING

A sensitive decision



When two sensory stimuli are presented sequentially, discriminating between them requires us to compare the second stimulus with stored information about the first one. A key problem is identifying the brain regions in which such an evaluation is made, and how they shape our subsequent behaviour. Focusing on the somatosensory system, Ranulfo Romo and his colleagues have obtained elegant evidence that a subset of neurons in the secondary somatosensory cortex (S2) participates in the comparison between past and present stimuli, implicating this brain region in the decision-making process.

The authors trained monkeys to discriminate which of two vibrating stimuli that were applied sequentially to their fingertips had the higher frequency, and to report their decision by pressing one of two buttons. Romo *et al.* recorded the activity of S2 neurons throughout the task, and found that, during the first stimulus, the cells merely encoded its frequency (f1). By contrast, during the second stimulus, the firing of some S2 neurons was not a simple function of f2, but depended on both the remembered and the current stimuli. So, for example, during the first few milliseconds of the second stimulus, the firing rates of some S2 neurons clearly depended on f1, despite the fact that the first stimulus had been presented as many as 3 seconds before. But during the final part of the second stimulus, firing depended on both f1 and f2. More precisely, the main determinant of firing was whether f2 was greater than f1, or f1 was greater than f2. Moreover, the behaviour of these S2 neurons during the final part of the second stimulus correlated with the monkey's choice, indicating that they might be involved in making a decision and reporting it to other parts of the brain for action.

Despite significant variability in the dynamics of the S2 responses during the second stimulus, the results of this study make a strong case for neurons in this area being involved in the comparison of the two stimuli and in the subsequent decision-making process. But as other brain areas, such as the prefrontal and the medial premotor cortices, also seem to have similar properties, it is likely that S2 is part of an extensive decision-related network. Future studies will allow us to disentangle more precisely the corresponding contributions of each of these structures to decision making.

Juan Carlos López

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PREFRONTAL CORTEX

One step at a time?

When I start to type this sentence, how does my brain represent the series of movements that are needed? Is each movement represented separately and in series, so that the representation of the movement needed to type the 't' of 'the' is followed by that for typing the 'h' and then the 'e', or does my brain 'plan ahead' and represent all of the letters in parallel? According to work by Averbeck *et al.*, the sequential movements are probably represented in parallel in my prefrontal cortex — at least, if I approach typing in the same way that a monkey approaches a serial motor task such as drawing a geometric shape.

The idea that sequences of movements are represented in parallel is not new. Fifty years ago, Lashley proposed that the serial order of movements — which must underlie many behaviours, including speech and locomotion, as well as typing — should be mediated by parallel response activation. This conclusion was based, in part, on the pattern of errors that Lashley observed in his own typing, and which will be familiar to any typist: the fingers seem to get ahead of themselves so that later letters are typed too soon (producing 'teh' rather than 'the'). Such errors indicate that serial movement patterns are represented in parallel, and sometimes 'selected' in the wrong order.

Averbeck *et al.* set out to find evidence for this idea in the monkey prefrontal cortex — an area of the brain that is important for the serial ordering of movement components. They recorded simultaneously from ensembles of neurons while the monkeys copied geometric shapes, such as triangles or squares, on a screen. The shapes were drawn as a sequence of segments, and the neural activity before and during each segment could be analysed. The authors were able to identify specific patterns of activity as representing each segment of the shapes. They found that all of the patterns were active before the monkey began to draw the shape, and that they all remained active during the process of drawing.

More interestingly, the strengths of the different representations evolved as the monkey drew the shape. At the beginning, the first segment was most strongly represented, but as this segment was drawn, its representation waned and the representation of the second segment became stronger. This process continued, so that each segment was the most strongly represented just before it was drawn. Presumably, this evolution of representations mediates the correct ordering of a sequence of movements.

The authors also looked at what happened when the monkeys made errors. Like humans, monkeys are most likely to make errors in the middle segments of serial tasks, rather than at the beginning or end. The first and last segments of each shape were more strongly represented than the middle segments, which might explain why the middle segments

were less likely to be drawn correctly. Furthermore, during error trials, the segment on which the monkey made the error was represented in the correct position on only 35% of trials, as opposed to 70% for correct trials. Instead, the subsequent section was more likely to be represented. Like typists, the monkey seemed to be getting ahead of itself.

The next step will be to look for similar patterns of activity in other areas of the brain. It will not be surprising if this method of representing serial order is a common feature, and it will be interesting to see how the interplay between different neural areas might contribute to the evolution of segment representations across time.

Rachel Jones

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IN THE NEWS

Ecstasy danger hits the headlines

There's nothing like a good scare story for getting neuroscience into the news, and this month's item is no exception. Step forward ecstasy (MDMA), the villain of the piece. The drug has been accused of causing brain damage that could lead to Parkinson's disease.

The study, by George Ricuarte and colleagues from Johns Hopkins University, tested the effects of several doses of ecstasy on monkeys' brains, designed to mimic the amount taken by a clubber in the course of a night. After six weeks, there were significant decreases in serotoninergic and dopaminergic markers. As dopaminergic innervation of the striatum declines with age, ecstasy users might be predisposed to develop Parkinson's disease later in life.

In the *Daily Telegraph* (UK, 27 September), Colin Blakemore of Oxford University says, "If dopamine cells are so dramatically affected… it's surprising that some people who have been using ecstasy for years are not already showing obvious signs of Parkinsonism. I think people would be well advised to avoid it."

However, the story is far from cut and dried. In the *Miami Herald* (5 October), Steven Kish of the Toronto Center for Addiction and Mental Health claims that "these studies are so flawed in terms of the technology used that one cannot derive any conclusion from them at all." Critics point out that the monkeys were injected with ecstasy, rather than taking it orally, and that 40% of the monkeys either died or suffered severe side effects. "How come 40% of people who are doing this drug are not dying or almost dying?" asked Rick Doblin of the Multidisciplinary Association for Psychedelic Studies.

Rachel Jones