ADDICTION

Appetite for drugs

Orexins, also known as hypocretins, are neuropeptides that are important for arousal, motivation, feeding and adaptive behaviours. In the mammalian brain, orexin-containing neurons in the lateral hypothalamus project to the ventral tegmental area (VTA) — a crucial site of synaptic plasticity induced by addictive drugs. Writing in *Neuron*, Borgland and colleagues show that, in rats, orexin A can potentiate glutamatergic neurotransmission of VTA dopamine neurons, and contribute to cocaine-induced behavioural changes.

From recordings of VTA neurons in rat midbrain slices, the researchers found that bath application of orexin A potentiated NMDA (*N*-methyl-D-aspartate) receptor-mediated excitatory postsynaptic currents. This effect was blocked by inhibitors of phospholipase C (PLC) or protein kinase C (PKC), suggesting the involvement of PLC/PKC-dependent intracellular pathways. Further pharmacological studies showed that orexin A potentiates mainly NR2A subunit-containing NMDA receptors, and the process requires translocation of intracellular NMDA receptors to the synapse.

Potentiation of NMDA receptors is crucial for the development of behavioural sensitization — a form of experience-dependent plasticity characterized by a long-lasting increase in drug-induced activation of locomotion, increased motivation for drug intake and enhanced drug reward. So, does orexin A also contribute to cocaine-induced effects? Systemic administration of SB334867, an antagonist of orexin receptor type 1 (OXR1, which has high affinity for orexin A), blocked cocaine-induced long-term plasticity at excitatory synapses on VTA dopamine neurons.

Systemic administration of SB334867 before cocaine injection attenuated the development of cocaine-induced behavioural sensitization, as measured by increased locomotor activity. Similar effects were observed when the inhibitor was directly microinjected into the VTA, suggesting that OXR1 activation at VTA dopamine neurons is responsible for cocaine-sensitization. However, application of the inhibitor at the end of cocaine treatment did not have any effect on the increase in locomotor activity, which indicates that orexin A is not required for the expression of behavioural sensitization.

In a previous study, the researchers showed similar findings with corticotropin-releasing factor (CRF). Therefore, orexin and CRF might mediate learned arousal and stress responses to the environment by regulating synaptic plasticity, and this neuroadaptive process could be 'hijacked' by drug abuse. Because arousal and stress can trigger drug-seeking behaviours, and as it is during periods of abstinence, rather than periods of intoxication, that addicts seek treatment, the peptide signalling pathways for orexin and CRF might be potential targets for the development of addiction medications.

Jane Qiu

ORIGINAL RESEARCH PAPER Borgland, S. L. *et al.* Orexin A in the VTA is critical for the induction of synpatic plasticity and behavioral sensitisation of cocaine. *Neuron* **49**, 589–601 (2006)

FURTHER READING Volkow, N. D. & Li, T. K. Drug addiction: the neurobiology of behaviour gone awry. *Nature Rev. Neurosci.* **5**, 963–970 (2004) | Ungless, M. A. *et al.* Corticotropin-releasing factor requires CRF binding protein to potentiate NMDA receptors via CRF receptor 2 in dopamine neurons. *Neuron* **39**, 401–407 (2003)

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SENSORY SYSTEMS

Connexin's auditory connection

Gap junctions — which contain intercellular channels composed of connexin proteins — allow molecules and ions to flow directly between most types of cell, and constitute electrical synapses between neurons. Mutations in connexin genes underlie approximately half of all cases of genetic deafness in childhood, but their modes of action are not well understood. A report in the *Journal of Neuroscience* provides new insights into the role of a recently identified connexin — CX29 — in auditory perception.

Four types of connexin, including CX29, are expressed in the cochlea. Tang and co-workers found that CX29 is abundantly and exclusively expressed in Schwann cells that myelinate the soma and processes of spiral ganglion neurons, which communicate sound signals transduced by hair cells to the cochlear nuclei in the brain stem. By contrast, the other connexins are primarily expressed in cochlear supporting cells and/or fibrocytes.

To determine the functions of CX29, Tang and colleagues studied mice that were deficient in *Cx29*. These mice were impaired in several aspects of auditory perception. Specifically, their hearing sensitivity across a range of frequencies was defective. In addition, they had sustained hearing loss for high-frequency sounds in response to stimulation with white noise, which resulted in only temporary impairments in wild-type mice.

The cochlear hair cells of these mice were morphologically normal, so what is the cellular mechanism that underlies these deficits? The presence of high levels of CX29 in Schwann cells suggested that myelination might be affected. Indeed, the myelin around the soma of spiral ganglion neurons was severely disorganized, although axonal myelin was normal.

CX29 is expressed in most Schwann cells and oligodendrocytes, yet only myelin in the spiral ganglion is affected in *Cx29*-knockout mice. Most myelinating glia express several connexin genes, each of which might compensate for the loss of another. However, these data suggest that spiral ganglion Schwann cells might express only CX29. Therefore, it seems that CX29 makes a unique contribution to myelination in the spiral ganglia and auditory perception.

This elegant study reveals the mechanisms by which CX29 plays its part in normal hearing. Moreover, the pattern of deficits in mice deficient in CX29 was consistent with that seen in patients with auditory neuropathies. Therefore, as the authors point out, these mice could provide a valuable model with which to explore the cellular and molecular basis of auditory neuropathy.

Alison Rowan

ORIGINAL RESEARCH PAPER Tang, W. *et al.* Connexin29 is highly expressed in cochlear Schwann cells, and it is required for the normal development and function of the auditory nerve of mice. *J. Neurosci.* **26**, 1991–1999 (2006)
FURTHER READING Söhl, G., Maxeiner, S. & Willecke, K. Expression and functions of neuronal gap junctions. *Nature Rev. Neurosci.* **6**, 191–200 (2005)

BEHAVIOURAL NEUROSCIENCE

Sniff and tell

Better known for their role in the adaptive immune response, genes of the major histocompatibility complex (MHC) also influence mating preference and social behaviour in vertebrates. Reporting in the *Journal of Neuroscience*, Spehr and co-workers show that non-volatile MHC peptides are recognized by olfactory sensory neurons in the main olfactory epithelium and transmit information used for social decision making in mice.

At least two anatomically and functionally distinct sensory organs allow mice to detect chemical signals: the vomeronasal organ, traditionally thought to transduce socially relevant chemical signals after direct contact with a source, and the main olfactory epithelium, a structure thought to detect only volatile molecules. The authors showed that during direct physical contact situations, such as sniffing and licking, non-volatile molecules could gain access to the main olfactory epithelium. Measurements of local field potentials showed a widely distributed sensitivity to remarkably low levels of non-volatile MHC peptides throughout this sensory tissue, whereas mutated control peptides did not elicit such highly sensitive responses.

> "…MHC peptides are recognized by … the main olfactory epithelium and transmit information used for social decision making in mice"

To identify the molecular mechanisms involved in transduction of peptide information, the authors disrupted elements of the evolutionarily conserved cyclic AMP (cAMP) second messenger system found in olfactory sensory neurons. Application of adenylyl cyclase antagonists or deletion of olfactory cyclic nucleotide-gated cation channels prevented the response of the main olfactory epithelium to MHC peptides, showing a requirement for cAMP signalling in the generation of peptide-evoked field potentials.

MHC peptides acting at the main olfactory epithelium were also shown to affect social preference of male mice *in vivo*. Male mice showed a preference for female urine from a different strain. Presented with identical female same-strain urine that had been supplemented with MHC peptides from either same-strain or different-strain mice, male mice showed a preference for urine containing MHC peptides from a different strain. This preference for disparate MHC peptides was also observed in mice lacking a functional vomeronasal organ, but was not seen in mice lacking olfactory cyclic nucleotide-gated cation channels or mice tested in a volatile-only paradigm.

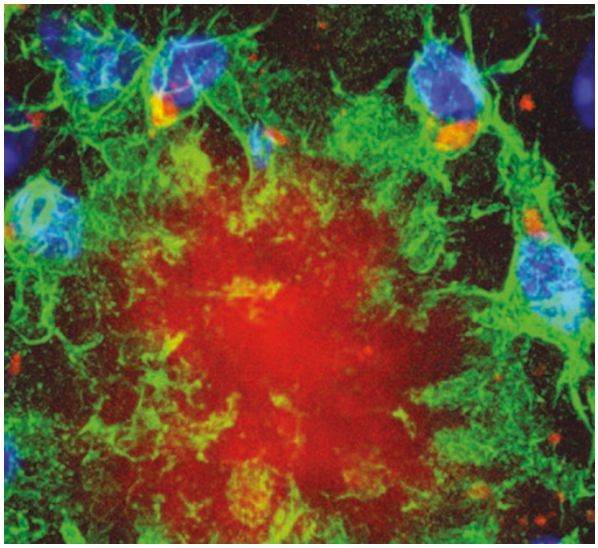
Taken together, these findings suggest that MHC peptides act as social recognition cues in mice that are detected by olfactory sensory neurons of the main olfactory epithelium and communicated by an evolutionarily conserved cAMP-dependent signalling pathway. These findings challenge the widely held view that the main olfactory epithelium detects only volatile molecules, and add to a growing body of evidence suggesting a much greater complexity of olfactory sensory systems.

Daniel McGowan

ORIGINAL RESEARCH PAPER Spehr, M. *et al.* Essential role of the main olfactory system in social recognition of major histocompatibility complex peptide ligands. *J. Neurosci.* **26**, 1961–1970 (2006)
FURTHER READING Dulac, C. & Torello, A. T. Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nature Rev. Neurosci.* **4**, 551–562 (2003)

NEURODEGENERATIVE DISORDERS

Microglia give amyloid plaques the brush off



Microglia (green) of bone marrow origin are attracted to the amyloid plaque (red) and clear amyloid-β by phagocytosis. Cell nuclei are stained blue. Image courtesy of S. Rivest, Laval University, Québec, Canada.

Microglia are the resident immune cells of the CNS and mount an immune response to any brain injury, including amyloid-β (Aβ) deposition in Alzheimer's disease. However, this immune response has been reported to both aggravate neurodegeneration and, by contrast, reduce Aβ deposition. So, do microglia help or hinder the development of Alzheimer's disease? Now, results reported by Simard and colleagues in *Neuron* suggest that microglia can protect against neurodegeneration, at least in a mouse model of Alzheimer's disease, and are recruited from bone marrow for this purpose.

Building on earlier research showing that bone marrow-derived cells can cross the blood–brain barrier, Simard and colleagues used a transgenic mouse model of Alzheimer's disease to determine whether microglia that associate with amyloid plaques are already resident in the brain or originate from blood. Transgenic mice were irradiated (to kill existing cells), and green fluorescent protein (GFP)-expressing bone marrow cells were then transplanted into their bloodstreams. The brains of these mice showed a massive infiltration of GFP-positive cells in the core of the amyloid plaques — that is, blood-derived microglia.

But what attracts blood-derived microglia to Aβ plaques? To answer this question, GFP-expressing bone marrow cells were injected into the bloodstream of wild-type mice after irradiation, followed 3 months later by a second injection of saline or different isoforms of Aβ directly into the hippocampus. Analysis of brain samples from these mice showed that only Aβ40 and Aβ42 trigger the attraction of microglia to Aβ deposits.

Compared with their brain-residing counterparts, microglia derived from the blood produce higher levels of proteins necessary for antigen presentation, which is part of the innate immune response, and so these microglia could be better phagocytes. Interestingly, the authors noticed

NEUROGENESIS

The window of fate

During development of the CNS, the generation of particular cell types from progenitor cells requires the tight regulation both of developmental transcription factors and of the progenitor cells' ability to respond to these factors (cell competence). Essentially, the transcription factors have a short window of opportunity — while the progenitors are competent — in which to govern their fate. However, it is not known whether competence is specific to individual transcription factors, or whether various factors can share a common competence window. Now, Cleary and Doe have begun to tackle this question, using the well studied NB7-1 neural progenitor cells of *Drosophila*.

The NB7-1 neural progenitor cell produces a series of ganglion mother cells (GMCs), each of which then divides to produce two neurons. The first five GMCs (GMC1–5) give rise to motor neurons (of the type U1–U5, respectively) and thereafter GMCs give rise to interneurons. The particular fates of the motor neurons are decided by the sequential expression, in NB7-1, of four transcription factors: Hunchback (HB), Krüppel (KR), PDM1/PDM2 (PDM) and Castor (CAS). HB specifies U1 and U2 neurons, KR specifies U3, PDM specifies U4, and PDM and CAS together specify U5.

Although HB and KR expression is only necessary for the first three motor neuron types (and, therefore, for the first three divisions to produce GMCs), Cleary and Doe investigated how long NB7-1 remained competent to both. They delivered pulses of either KR or HB to NB7-1 just before the birth of each GMC and then looked for the production of U1, U2 or U3 motor neurons. They found that both factors could induce their respective neurons up to the fifth division (production of GMC5), after which competence to both was lost. This therefore indicated that HB and KR share a window of competence.

that many blood-derived microglial cells contained small deposits of Aβ, and these deposits were located in specific subcellular compartments of the microglia. This led the authors to suggest that these microglia, and not resident microglia, can act as phagocytes for Aβ, a proposal that was confirmed using cultured microglia treated with Aβ42.

Simard and colleagues have shown that blood-derived microglia can actively reduce Aβ deposits and so slow the progression of Alzheimer's disease. It will be interesting to see whether increasing the number of blood-derived microglia in the brain of these transgenic mice will improve cognitive performance, as this would have significant implications for the development of a therapeutic treatment for Alzheimer's disease.

Samantha Barton

ORIGINAL RESEARCH PAPER Simard, A. R. *et al.* Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* **49**, 489–502 (2006)

In further experiments, the team prolonged the expression of HB and KR, and showed that, by doing so, it was possible to prevent the production of U4 and U5 cells. The authors' interpretation of this finding was that by the time HB or KR expression had stopped, the production of U4 and U5 neurons was no longer possible — PDM and CAS had essentially missed their window of opportunity.

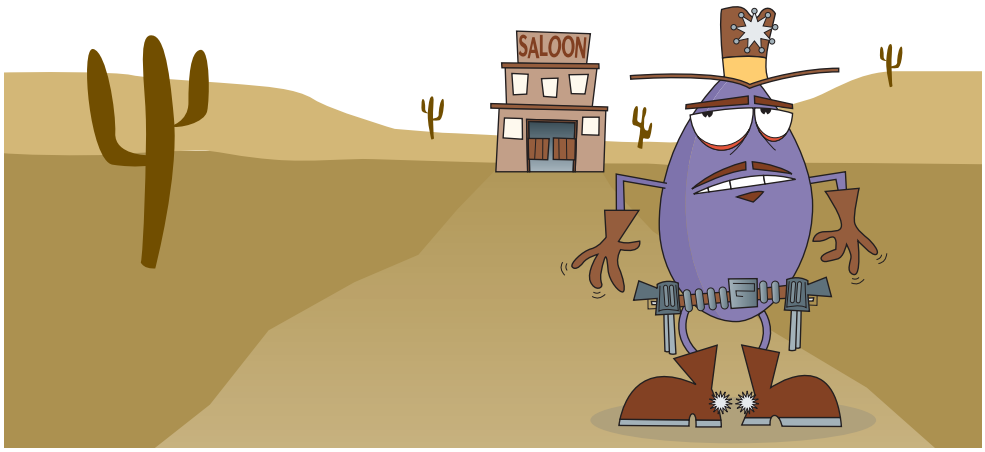
Together, Cleary and Doe's findings indicate that all four transcription factors share the same competence window (lasting five GMC divisions). It remains to be discovered which mechanisms define this window and what, after five divisions, closes the curtains on competence.

Ruth Williams

ORIGINAL RESEARCH PAPER Cleary, M. D. & Doe, C. Q. Regulation of neuroblast competence: multiple temporal identity factors specify distinct neuronal fates within a single early competence window. *Genes Dev.* **20**, 429–434 (2006)

BEHAVIOURAL NEUROSCIENCE

The good, the bad and the amygdala



Ever feel hungry when you see a picture of a burger? Or annoyed when you see a particular politician? Such conditioning to visual stimuli is key to many aspects of emotion, learning and behaviour. Although a great deal is known about how the brain processes and analyses visual information, we have little understanding of how visual stimuli become linked with positive or negative emotions (value). Reporting in *Nature*, Salzman and colleagues show that, in the brains of monkeys, values associated with visual stimuli are represented in the amygdala — a structure implicated in reinforcement learning — and that individual amygdala neurons code for either 'good' or 'bad'.

The amygdala is known to receive both inputs from the visual system and reinforcing stimuli from other sensory systems, making it a good candidate for the site of visual stimulus value representation in the brain. To investigate this potential role, Salzman's team recorded the electrical activity of individual amygdala neurons while monkeys were conditioned to associate particular images with positive or negative outcomes. The monkeys learned to lick in anticipation of the positive outcome, a liquid reward, and to blink in anticipation of the negative outcome, which was an aversive air-puff. To look for neurons that might be value-encoding, rather than just firing in response to visual stimuli, the team switched the outcome for a particular image half way through the trials (images originally associated with reward became associated with a negative outcome and vice versa). They found that more than 50% of amygdala neurons showed a switch in activity, and also that individual neurons showed value-specific activity. Therefore, the amygdala is a site rich in visual value-encoding neurons and, interestingly, these individual neurons encode either positive or negative value.

To investigate the link between neural activity and the conditioned behavioural response (licking or blinking), the team measured the time taken for both to change, following the switch in image value outcome. Neural activity changed rapidly (after just a few trials) and, importantly, this coincided almost exactly with a change in conditioned behaviour. This tight link strongly argues for the amygdala as a primary brain area for learning the value of visual stimuli. Interestingly, some neurons changed their activity in advance of behavioural changes. The authors therefore suggest that the monkeys are unable to selectively 'listen' to individual neurons, but instead must interpret signals from 0a population.

This important work by Salzman's group not only confirms that the amygdala is a key brain structure in the representation of the learned value of visual stimuli, but also suggests how this representation is interpreted. The next aim will be to add to our understanding of how the amygdala communicates with other brain structures and plays its part in the complex neural circuitry that controls the learning, emotion and behavioural networks.

Ruth Williams

ORIGINAL RESEARCH PAPER Paton, J. J. *et al.* The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* **439**, 865–870 (2006)

In the news

WORKING OUT FOR BRAINY BABIES

Whether it is best for pregnant mothers to rest or to exercise is a frequently asked question that a study in mice may go some way towards answering. Increased neuronal production resulting from exercise has previously been shown in adult rodents, and, says Gerd Kempermann, who led a study on the effects of exercise during pregnancy on mouse pups at the Max Delbrück Center for Molecular Medicine in Berlin, Germany, "Now we've established that it seems to be transmissible to offspring" (*New Scientist*, 11 March 2006).

Kempermann and his team showed that although pups born to mice that had been active during pregnancy developed fewer neurons prenatally, they then developed up to 40% more hippocampal neurons — which are vital for learning and memory — during the first few weeks after birth than did the pups of inactive mothers. By 7 weeks of age, the difference in neuronal production rate had balanced out, but the researchers propose that the early variation could have long-term effects.

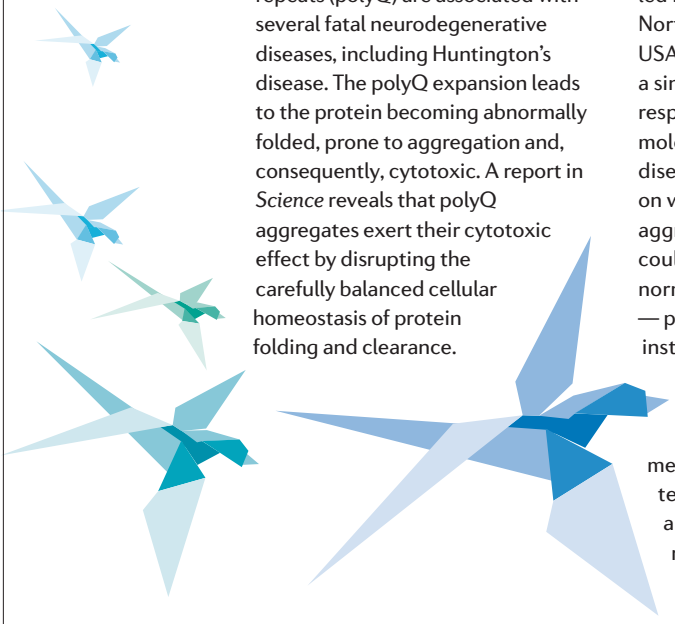
These results, says Kempermann, are "surprising and amazing" (*News@Nature.com*, 6 March 2006), although he acknowledges that we cannot assume that exercise during pregnancy has similar effects in humans.

The reasons for the variations in neuronal production are unknown, and given that exercise produces stress hormones, and that stress during pregnancy is known to depress neuronal production in mouse pups, these results are surprising. It could be that a combination of factors is involved. For example, exercising mothers may be healthier, and other differences in their behaviour — such as increased licking and grooming — might stimulate neuronal production in their newborn pups. As Elizabeth Gould, who studies neuronal production at Princeton University in New Jersey, USA, says, "There's not just one magic bullet" (*News@Nature.com*).

Sarah Archibald

NEURODEGENERATIVE DISEASES

Folding failure



Proteins with expanded glutamine repeats (polyQ) are associated with several fatal neurodegenerative diseases, including Huntington's disease. The polyQ expansion leads to the protein becoming abnormally folded, prone to aggregation and, consequently, cytotoxic. A report in *Science* reveals that polyQ aggregates exert their cytotoxic effect by disrupting the carefully balanced cellular homeostasis of protein folding and clearance.

Various mechanisms have been proposed to explain the cytotoxic effects of polyQ aggregates. These include the disruption of cellular processes such as transcription, energy metabolism and protein folding, and the activation of apoptosis. These varied proposals led Richard Morimoto's team at Northwestern University, Illinois, USA, to ask whether there might be a single general mechanism responsible for triggering the molecular pathology of the polyQ diseases. Specifically, they focused on whether expression of an aggregation-prone polyQ protein could affect the folding stability of normal cellular metastable proteins — proteins with a tendency towards instability.

Temperature-sensitive mutant proteins provide a useful genetic model of such metastable variants. At permissive temperatures they convey no abnormal phenotype, but at raised, restrictive temperatures the metastable balance is tilted, and the proteins misfold and fail to

ION CHANNELS

Behind closed pores

Voltage-gated ion channels maintain membrane resting potentials and generate action potentials by regulating ion flux. A recent article published in the *Proceedings of the National Academy of Sciences* provides evidence that ether-à-go-go (EAG) K^+ channels can also regulate intracellular signalling pathways by a mechanism independent of ion flux.

Hegle and co-workers noticed that transfection of fibroblasts with *Drosophila eag* led to an increase in cell density, prompting them to quantify proliferation. They observed a dramatic increase in bromodeoxyuridine incorportation in myoblasts and fibroblasts following transfection with *eag*, an effect not seen in cells transfected with the gene for another voltage-dependent K^+ channel, Shaker. This effect was independent of ion flux, as point mutations that eliminate conduction did not prevent EAG-induced proliferation.

> "EAG channels … regulate intracellular signalling pathways … independent of ion flux."

The authors then investigated which intracellular signalling pathways were regulated by EAG. Mitogen-activated protein (MAP) kinases, such as p38 and ERK1/2, have a major role in signal transduction from the cell surface to the nucelus and are central to proliferation in several cell types. Two inhibitors of p38 MAP kinase blocked EAG-induced proliferation, whereas an inhibitor of ERK1/2 did not. In addition, there was a twofold increase in the level of activated (phosphorylated) p38 in cells expressing either conducting or non-conducting EAG channels, providing further confirmation that this kinase is involved in EAG-induced proliferation.

Although EAG signalling is independent of ion flux, an increase in extracellular K^+ concentration, to levels that depolarize the membrane, inhibited EAG-induced proliferation. Because depolarization induces a shift in the position of the voltage sensor — a transmembrane helix present in all voltage-gated ion channels that detects voltage and transfers its energy to the pore — the authors proposed that the position of this helix is important for EAG signalling. To test this, mutations

function. The group used various temperature-sensitive *Caenorhabditis elegans* strains and crossed them with transgenic lines expressing polyQ proteins. Normally, temperature-sensitive strains show their defective phenotype only at restrictive temperatures. However, when crossed with the polyQ worms the defective phenotype became apparent even at permissive temperatures.

So how were the polyQ proteins prompting the metastable proteins to misfold? Closer examination of one particular temperature-sensitive strain revealed that the abnormal crystalline structures usually formed by the misfolded protein at restrictive temperatures were also being formed in the temperature-sensitive/polyQ worms. This suggested that the polyQ protein did not exert its effect through specific interactions or aggregations with the metastable protein itself, but rather put stress on the general cellular protein folding machinery. With this in mind, the team supposed that the level of aggregation of the polyQ protein would also be increased (by positive feedback) in the temperature-sensitive/polyQ worms — and it was.

From this work the authors suggest a model whereby under normal conditions misfolding of metastable cellular proteins is adequately dealt with by the protein folding and clearance machinery. However, the expression of aggregation-prone polyQ proteins overwhelms the machinery and disrupts the homeostatic balance. It interferes with the folding environment of the cell, which, in turn, leads to the gradual accumulation of misfolded proteins, and to disease. Therefore, therapies that target this folding problem might hold promise for future polyQ disease treatment.

Ruth Williams

ORIGINAL RESEARCH PAPER Gidalevitz, T. *et al.* Progressive disruption of cellular protein folding in models of polyglutamine diseases. *Science* 9 Feb 2006 (doi:10.1126/science.1124514)

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that produce hyperpolarizing shifts in the voltage-dependent activation of EAG channels were combined with the mutation eliminating conduction, and non-conducting, predominantly open EAG channels were found to be unable to induce proliferation. Conducting, predominantly open channels induced proliferation similar to that of wild-type channels due to the negative feedback of conduction on channel conformation. These findings show that the voltage-sensitive conformation of this channel might act as a switch for EAG signalling activity.

Although similar bifunctional properties have previously been ascribed to Ca^{2+} channels, this is the first description of a bifunctional K^+ channel that can influence the activity of intracellular messengers independent of flux. Given the importance of MAP kinases in synaptic plasticity and learning, it will be informative to determine whether the link between p38 activity and EAG is conserved both in neuronal cells and *in vivo*.

Daniel McGowan

ORIGINAL RESEARCH PAPER Hegle, A. P. *et al.* A voltage-driven switch for ion-independent signalling by *ether-à-go-go* K^+ channels *Proc. Natl Acad. Sci. USA* **103**, 2886–2891 (2006)

IN BRIEF

BEHAVIOURAL NEUROSCIENCE

Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood.

Weaver, I. C. G. *et al. Proc. Natl Acad. Sci. USA* **103**, 3480–3485 (2006)

In rats, the level of maternal care given can affect the anxiety experienced by the adult offspring. The results of previous research suggested that this might be due to epigenetic regulation of the glucocorticoid receptor (*Gr*) gene. Glucocorticoids are involved in dampening the stress response, and in offspring that have received a high level of maternal care *Gr* expression is increased. Therefore, in stressful situations, these rats show less fearful behaviour than those whose mothers were neglectful. A new genome-wide study shows that, in fact, more than 900 genes are differentially expressed in the hippocampus as a result of maternal care. Among these genes are *Atrx* and *Vof16* (both of which are involved in neurodegeneration) and reelin (an extracellular matrix protein thought to control cell–cell interactions that are crucial for neuronal migration during brain development). This study will contribute to the elucidation of potential pathways and mechanisms that link maternal care to subsequent adult behaviour.

GLIA

Neuron to glia signalling triggers myelin membrane exocytosis from endosomal storage sites.

Trajkovic, K. *et al. J. Cell Biol.* 6 March 2006 10.1038/jcb.200509022

The myelin sheath, which encircles neuronal axons and is essential for their rapid impulse conduction, is formed from extensions of the plasma membrane of oligodendrocytes. Development of this specialized membrane is known to be induced by signals from neurons, but how are these signals interpreted? Now a study by Trajkovic *et al.* shows that neuron to oligodendrocyte signalling promotes deposition of the myelin protein, proteolipid protein (PLP), at the oligodendrocyte membrane through both increasing exocytosis and reducing endocytosis of PLP-containing vesicles.

SENSORY SYSTEMS

Pax6-dependent boundary defines alignment of migrating olfactory cortex neurons via the repulsive activity of ephrin A5.

Nomura, T. *et al. Development* 1 March 2006 10.1242/dev.02290

The developing telencephalon (anterior forebrain) is divided into two domains: the pallium and the subpallium. PAX6 is a key developmental transcription factor that has been suggested to have a role in establishing the boundary between the two. Now, Nomura *et al.* report in *Development* that, in mice that are mutant for *Pax6*, olfactory neurons migrating from the dorsal pallium overshoot their target and continue to migrate into the ventral subpallium. The team also found that ephrin A, a protein implicated in axon repulsion, was markedly reduced in *Pax6* mutant mice, and that expression of exogenous ephrin A could reverse the mutant phenotype and set olfactory neurons back on the right track.

NEUROLOGICAL DISORDERS

Keeping pace with ataxia

Episodic ataxia type 2 (EA2) is a rare form of inherited ataxia, characterized by attacks of incoordination and migraines. This disorder is caused by mutations in the P/Q type of voltage-gated calcium channel, which is widely expressed in presynaptic terminals of many neurons. These channels are especially abundant in the Purkinje neurons of the cerebellum, a brain area known to be crucial for motor coordination. Writing in *Nature Neuroscience*, Walter and co-workers now provide an explanation for how P/Q channel deficits cause irregular firing of Purkinje neurons, and how this, in turn, leads to ataxia.

Under normal circumstances, Purkinje cells spontaneously fire continuously (at rates of ~40 Hz). This pacemaking activity is regulated mainly by small (SK) and large (BK) conductance calcium-activated potassium channels. P/Q channels activated during an action potential recruit SK channels, which stay active between spikes. This, in turn, generates a conductance that contributes to the hyperpolarization of the membrane potential between action potentials; recruitment of the depolarizing channels that drive the next spike requires these well-timed hyperpolarizations.

These researchers took advantage of rodent models of EA2 known as leaner, tottering and ducky. Each of these mouse strains has an ataxic phenotype due to mutations in the P/Q channel gene. Using recordings from cerebellar slices, they found that in both ducky and leaner mice, the precision of the intrinsic pacemaking of the Purkinje cells was reduced without affecting the mean firing rate of Purkinje cells. They also found that the erratic pacemaking of Purkinje cells in these mutant mice reduced the accuracy of the Purkinje cells in encoding and transmitting the synaptic information they receive from the cerebellar cortex to neurons of the deep cerebellar nuclei.

To prove that the irregular firing of Purkinje neurons causes an ataxic phenotype, the authors used 1-ethyl-2-benzimidazolinone (EBIO), a drug that increases the affinity of SK channels for calcium. This drug did not alter the firing pattern of wild-type neurons, but made the mutant neurons fire more regularly. Chronic perfusion of EBIO into the cerebella of ducky and tottering mice improved their performance on an accelerating motor rod (a standard test for motor coordination) and reduced both the frequency and severity of dyskinesic attacks that these mice experienced. Importantly, EBIO did not affect wild-type mice.

These findings not only provide a mechanistic explanation for how mutations in P/Q channels can cause ataxia, but also identify a new target for future therapeutic approaches for EA2. There are some differences between the mouse models of EA2 and human patients with EA2 — the patients have other non-cerebellar symptoms, such as muscle weakness, and we do not yet know if human patients suffer from irregular Purkinje cell firing. Whether EBIO or other SK channel modulators will work their magic in human patients remains to be seen, but Walter *et al.* have provided the blueprint for future studies on this topic.

Kalyani Narasimhan, Senior Editor
Nature Neuroscience

ORIGINAL RESEARCH PAPER Walter, J. T. *et al.* Decreases in the precision of Purkinje cell pacemaking cause cerebellar dysfunction and ataxia. *Nature Neurosci.* **9**, 389–397 (2006)
FURTHER READING Otis, T. S. & Jen, J. C. Blessed are the pacemakers. *Nature Neurosci.* **9**, 297–298 (2006)

NEUROIMMUNOLOGY

Damage versus repair

Complement, a component of the humoral immune system, is expressed by many cell types of the CNS. The role of complement in normal CNS function is unknown, but in disease or injury, such as ischaemia, complement activation contributes to the inflammatory response and, therefore, to resulting tissue destruction. However, new work from Marcela Pekna's laboratory identifies an additional and opposite role for complement in adult neurogenesis and ischaemia-induced repair.

Recent evidence from diverse sources has implicated the complement system in tissue regeneration. For example, in amphibians, C3 (third complement component) expression has been detected in regenerating limbs, and in newts both C3 and C5 (fifth component) have been detected in regenerating limbs and lenses. Furthermore, in mammals, C3 and C5 are both involved in hepatocyte proliferation and liver regeneration. These findings led Pekna's team to wonder if complement might have a role in adult neurogenesis.

Neurogenesis occurs as a normal function of the adult brain and becomes exaggerated in response to injury. First, the team investigated normal neurogenesis and found that mice deficient for C3, or its cell surface receptor C3AR, had a reduced number of newly formed and migrating neurons — indicating impaired neurogenesis. Next, to look at injury repair, the team artificially induced ischaemia and found that C3-deficient mice also had fewer new neurons at the repair site than wild-type mice. Importantly, these researchers showed that this reduction in ischaemia-induced neurogenesis was not due to a decreased injury size (as might occur as a result of reduced inflammation in the absence of C3).

It is surprising that complement can, on the one hand, be involved in inflammation and associated tissue damage, and, on the other hand, support neurogenesis and migration of new neurons. A better understanding of how these two opposing roles are balanced in the CNS might lead to therapies that can tip the scales in favour of repair.

Ruth Williams

ORIGINAL RESEARCH PAPER Rahpeymai, Y. *et al.* Complement: a novel factor in basal and ischemia-induced neurogenesis. *EMBO J.* 23 February 2006 (doi: 10.1038/sj.emboj.7601004)