Maternal behaviour during development can have a powerful influence on stress levels of the offspring later in life as a result of lasting epigenetic modifications. According to work published in *The Journal of Neuroscience*, it now seems that just as gene expression can be altered during development, it can also be altered later in life to reverse these modifications.

Stress responses are mediated by regulation of the hypothalamic–pituitary–adrenal (HPA) axis: neural stimulation causes release of corticotropin-releasing factor (CRF), which activates the HPA axis, whereas glucocorticoid feedback blocks synthesis and release of CRF, thereby reducing HPA responses to stress.

Adult rats that have experienced high levels of maternal care — measured by the extent of licking and grooming behaviour — during the first week of life have reduced levels of hypothalamic CRF and lower HPA responses to stress in adulthood compared with those that have received relatively low levels of maternal care early in development. Cross-fostering studies suggest that this effect is due to maternal behaviour and not to genomic transmission of stress responses. The epigenetic mechanism that underpins these differences involves changes in the methylation state of the hippocampal glucocorticoid receptor promoter: in animals that have received high levels of maternal care, this promoter is hypomethylated, whereas lower levels of maternal care are associated with hypermethylation of this promoter.

To test the possibility that these DNA methylation patterns can be reversed, Weaver and colleagues infused methionine — a well-known dietary modulator of DNA methylation — into the brains of adult rats that had received either high or low levels of maternal care. Increased methionine levels induced hypermethylation of the glucocorticoid receptor promoter in rats that had received high levels of maternal care, which did indeed reverse the effects of maternal behaviour in early development on glucocorticoid receptor expression and the HPA response to stress in adult life. These results suggest that the enzymatic mechanisms that underlie DNA methylation and demethylation can be activated not only during development but also in adult postmitotic hippocampal neurons. Stable epigenetic changes therefore seem to be susceptible to plasticity in adulthood.

Dietary methionine is essential for normal brain development, and abnormalities in DNA methylation have been linked to some neurological disorders, such as fragile X syndrome, and several psychiatric conditions, including schizophrenia. As Weaver et al. speculate, these data raise the intriguing possibility that epigenetic modifications during development and adulthood could be influenced by dietary modification of methylation, and might offer a potential therapeutic avenue for the treatment of a range of disorders of the nervous system.

Alison Rowan
The social deficits associated with autism, which include difficulty communicating and understanding environmental cues, such as facial expression, have been extensively reported. However, the neural mechanisms behind the disorder remain in question. One proposed culprit is the mirror neuron system, which is thought to be involved in interpreting the emotions of others. Further support for this idea has now been provided by a group of US scientists, who have shown that activation of the mirror neuron system is much reduced in the brains of children with autism.

Neuroscientists believe that mirror neurons fire in response to the facial expressions of others, allowing our brains to ‘mirror’ their actions and so understand their feelings. Mirella Dapretto, who led the research at the University of California, Los Angeles, USA, said, “The mirroring mechanism may underlie the remarkable ability to read others’ emotional states from a mere glance” (Guardian, 6 December 2005). “Our findings suggest that a dysfunctional mirror neuron system may underlie the social deficits observed in autism. This is exciting because we finally have an account that can explain all core symptoms of this disorder” (Guardian).

The researchers observed not only that activation in the brain area containing mirror neurons — the inferior frontal gyrus pars opercularis — was reduced in children with autism, but also that the extent of the decrease in activation correlated with the severity of symptoms. Michael Rutter of the Institute of Psychiatry, London, UK, agreed that “The general notion of linking mirror neurons with the social deficit in autism is quite reasonable” (BBC News Online, 5 December 2005). However, he also observed “…we need more research into the brain systems that might be involved. These might involve mirror neurons, but we need more studies” (BBC News Online).

Sarah Archibald
Sen et al. studied the effects of expression of a dominant-negative form of the human RA receptor α in the developing chick retina. Blocking RA activity in this way resulted in a lack of ventral expression of EphB2 and EphB3 and dorsal expression of ephrin B2. Moreover, loss of RA activity did not affect expression of the transcription factor VAX, which is also involved in regulating EphB receptors and ephrin B ligands. However, misexpression of VAX resulted in loss of or ectopic expression of RA-synthesizing enzymes.

These findings suggest that RA acts in parallel with or downstream of VAX activity, and that it is crucial for controlling the expression of EphB/ephrin B molecules to form a topographic map of the dorsoventral retina during development.

Alison Rowan


This finding is striking because specific neuronal loss in area CA1 is associated with cognitive decline in Alzheimer’s disease. It will now be important to establish the physiological relevance of heterogeneity in the concentration dynamics of NO along the trisynaptic loop of the hippocampus.

Samantha Barton


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**NEURODEGENERATIVE DISORDERS**

A central role for α-synuclein in neurodegenerative conditions has long been apparent: mutations or triplication of the gene cause severe Parkinson’s disease, and inclusion bodies containing the protein are found in Parkinson’s disease, Alzheimer’s disease and other neurodegenerative ‘synucleinopathies’. However, despite its involvement in pathology, the normal physiological function of α-synuclein, which is enriched in presynaptic nerve terminals, has remained an enigma. New work from the laboratory of Thomas Sudhof reveals an unexpected neuroprotective role for α-synuclein in a progressive neurodegenerative mouse model caused by deletion of cysteine-string protein-α (CSPα).

CSPα is a molecular chaperone, abundant at presynaptic nerve terminals, deletion of which results in early-onset neurodegeneration and lethality in mice by 1–4 months of age. Similarly, overexpression of human α-synuclein leads to a progressive, but late-onset, neurodegenerative phenotype. Intrigued by an apparent overlap in the localization of α-synuclein and CSPα, and a possible complementarity of their functions, Chandra and colleagues investigated the relationship between the neurodegenerative phenotypes associated with each protein, crossing transgenic α-synuclein mice with CSPα-knockout mice.

Interestingly, expression of the α-synuclein transgene abrogated the lethality and neurodegeneration caused by the CSPα knockout. Moreover, the weight loss, gliosis, and progressive loss of muscle strength and muscle coordination observed in CSPα-knockout mice were abolished by expression of human or mouse wild-type α-synuclein, or A53T mutant human α-synuclein. However, A30P mutant human α-synuclein, which has a much reduced ability to bind phospholipids, was unable to rescue the CSPα-knockout phenotype, suggesting that attachment of α-synuclein to synaptic vesicles is essential for its neuroprotective function. Impaired SNARE complex assembly observed in CSPα-knockout mice was also rescued by wild-type or A53T α-synuclein, but, again, no protection was observed with A30P α-synuclein.

Given the apparent neuroprotection provided by exogenous overexpression of α-synuclein in this model, Chandra and co-workers investigated the possibility that endogenous synucleins might partially protect against an even more severe phenotype. In support of this scenario, α/β-synuclein double knockout, which alone exhibits no phenotype, resulted in exacerbation of the CSPα-knockout phenotype, accelerating lethality and neurodegeneration. An intermediate phenotype was observed in mice lacking CSPα and α-synuclein, which indicates some redundancy between synuclein isoforms.

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Differences in the cell-specific expression patterns of α-synuclein and CSPα revealed that α-synuclein is protective only of neurons in which it is expressed: photoreceptor cells lacking transgene expression degenerate in CSPα-knockout mice, and ‘rescued’ mice show deficits in tests requiring normal eyesight. No physical interaction could be observed between α-synuclein and either CSPα or its binding partners, nor was a physical interaction could be observed between α-synuclein and either CSPα or its binding partners, nor was α-synuclein able to substitute for CSPα in stimulating heat shock cognate 70 (HSC70) ATPase activity, suggesting that α-synuclein acts through a mechanism downstream of CSPα to protect against the consequences of its absence, rather than merely substituting for loss of CSPα function. Furthermore, the neuroprotective capability of α-synuclein was specific to the deficits induced by CSPα knockout, as no rescue was seen in a separate (mutant superoxide dismutase) model of neurodegeneration.

Although the significance of these findings to patients with Parkinson’s disease are not yet clear, and further dissection of the molecular mechanisms involved in synuclein-induced neuroprotection will certainly be required, knowledge of the physiological role of α-synuclein will provide a much-needed insight into its parallel pathogenic role.

Daniel McGowan

**SYNAPTIC PHYSIOLOGY**

**A barrier to diffusion**

Stimulation of excitatory neurons triggers the movement of calcium into dendritic spines and the build up of second messengers in the spine head, which, in turn, activates regulatory signalling cascades that underpin alterations in the strength of excitatory synapses. The level of signalling molecules in the spine head is therefore crucial for the induction of synaptic plasticity, and Bloodgood and Sabatini have shown recently that the spine neck has a dynamic role as a diffusion barrier in regulating the movement of these molecules into and out of the spine head.

These researchers combined two-photon laser-scanning microscopy with two-photon laser photoactivation to measure regulation of diffusion of the photoactivatable green fluorophore PAGFP, which is similar in size to many proteins that are involved in synaptic modification, across spine necks in individual pyramidal neurons of the rat hippocampus. They showed that there are substantial variations in the time taken for diffusion across the spine neck among different spines, whereas within individual spines there was a high degree of consistency in these values.

In a subset of spines, there was very little movement across the spine neck, indicating that this structure can act as a barrier to diffusion, effectively isolating the spines from the dendrites. Repeated measurements over long time periods showed that this effect is reversible, which indicates that the diffusion barrier imposed by spine necks is dynamic and not static.

Bloodgood and Sabatini proposed that the variations in rate of diffusion are therefore crucial for the induction of excitatory synapses. The level of diffusion of second messengers in the spine neck, the length of the neck or the spine head, the cross-sectional area of the neck, and the volume of the spine head all have important roles in regulating the movement of these molecules into and out of the spine head.

**NEUROGENETICS**

**Fear not**

Fear helps animals — including humans — to survive, as it allows them to avoid predators and dangerous situations. However, too much fear, or inability to control it, can be detrimental and result in phobias, pathological anxiety or post-traumatic stress disorder. The identification of the gene stathmin as an important mediator of both instinctive and learned fear is therefore crucial for fear processing — the researchers set out to study whether these genes have a role in fear.

Writing in Cell, they show that mice lacking stathmin are fearless daredevils. Knockout mice do not seem to have instinctive fear, venturing bravely into potentially dangerous environments, such as open fields or elevated platforms, which normal mice would usually avoid.

Stathmin-knockout mice also have weaker memories for past aversive experiences. Shumyatsky et al. tested this using the fear conditioning paradigm. During training, mice were given a conditioned stimulus (a loud tone), which was immediately followed by an unconditioned one (a mild electric footshock). Normal mice make an association between the stimuli and freeze up when they hear the tone during testing the next day. However, the stathmin-knockout mice performed poorly in this test, which indicates that they are inept at forming fear-related memories.

To ensure that this was not due to changes in other features that might have resulted from lack of the gene, the researchers tested the mutant animals’ sensitivity for pain. It was normal, as was their performance in spatial memory, which indicates that the effect of stathmin on learned fear is genuine and specific.

How does stathmin affect fear-related memory? It turns out that stathmin can inhibit the dynamics of microtubule formation. Microtubules in the amygdala crossroad where sensory information is transmitted from the auditory cortex and auditory thalamus to the amygdala — a crucial process for fear processing. The researchers tested the mutant animals’ sensitivity for pain. It was normal, as was their performance in spatial memory, which indicates that the effect of stathmin on learned fear is genuine and specific.

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the diffusion coefficient of the molecules, accounted for the effects of activity on diffusion rates. Moreover, in experiments that involved the green-fluorescing pyranine-based fluorophore HPTS, which is similar in size to second messengers such as cyclic AMP, diffusion across the spine neck was further restricted by pairing synaptic stimulation with back-propagating action potentials.

These findings support an important and dynamic role for the spine neck in the regulation of movement of second messengers and activated proteins into and out of the spine head, and therefore in the induction of synaptic plasticity. It is hoped that future work will reveal the factors that directly influence constriction or expansion of spine necks.

Alison Rowan


of the mutant mice are more stable (less flexible) compared with those of their normal counterparts. As new memories involve the formation of new synapses, which may require assembly and disassembly of microtubules, the researchers conjecture that this might explain why mice lacking stathmin cannot effectively form fear-related memories. Consistent with this hypothesis, there was a significant decrease in long-term potentiation in the amygdala pathways of mutant mice.

It is hoped that future work will reveal the factors that directly influence constriction or expansion of spine necks.

Jane Qiu


The turning point

Engrailed 2 (En2), a homeodomain transcription factor, is expressed in a caudal-to-rostral gradient in the developing tectum. This is thought to be crucial for setting up the gradients of axon guidance cues that are important for topographic map formation in the vertebrate visual system. However, the results of a new study show that En2 can also affect axon turning by interacting with the translational machinery in the growth cone.

En2 contains a few protein domains involved in nuclear export, secretion and internalization, and can be secreted and transferred from one cell to another. These features are unorthodox for a transcription factor and have long intrigued researchers. Brunet and colleagues set out to solve this mystery and tested the effect of an En2 gradient on axon turning in vitro.

Interestingly, Xenopus nasal axons were attracted by En2, whereas temporal axons were repelled. These opposite turning responses correspond to the in vivo organization of the retinotectal map, in which nasal axons terminate in the En2-rich caudal tectum but temporal axons avoid it. En2 was rapidly internalized by living growth cones. This process seems to be crucial for the effect of En2 on axon turning, as a mutant form of En2 that was defective in internalization also had no effect on growth cones.

Next, the researchers studied whether the turning responses required involvement of the cell body and whether gene expression and protein synthesis were necessary. Nasal growth cones transected from their cell bodies still turned towards an En2 gradient, and isolated temporal growth cones continued to turn away from this gradient. These responses were blocked by protein synthesis inhibitors, but not transcription inhibitors, which indicates that nascent protein synthesis in the growth cone is necessary for its turning responses to En2.

But how does En2 regulate the translational machinery in the growth cone? Like many other homeodomain proteins, En2 contains a highly conserved binding site to erkaryotic initiation factor 4E (eIF4E) that is typically found in translational machinery. En2 can bind to eIF4E, and Brunet et al. showed that a mutant form of En2 that lacks the putative eIF4E-binding domain did not attract nasal axons. In addition, En2 triggered rapid phosphorylation of eIF4E and eIF4E-binding protein (4E-BP1). It is thought that 4E-BP1 silences translation by competitively binding to eIF4E and sequestering it from the translation initiation complex. Phosphorylation of 4E-BP1 releases eIF4E, which, on phosphorylation, becomes activated and initiates translation.

This elegant study has unravelled a new mechanism whereby the concentration gradient of En2 is used to guide axon growth. Whether other transcription factors have a similar role remains to be seen.

Jane Qiu


Web Site Holt’s laboratory: http://www.anat.cam.ac.uk/staff/holt/
Sniffing out neural processing

A good sense of smell and olfactory memory are important to many animals for prey and predator recognition, and so are vital for survival. Through variable expression of a glutamate receptor subunit, Shimshek and colleagues have further elucidated where and how the processes responsible for these faculties occur. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (AMPARs) are crucial for learning and memory. At the neuronal level, both odor discrimination and olfactory memory depend on fast excitatory neurotransmission mediated by these receptors. Shimshek and co-workers investigated the involvement of the principal AMPAR subunit, GluRB (GluR2), in these processes by depleting it or expressing a mutant form in mice. Both groups of mice showed specific increases in olfactory discrimination, but, surprisingly, a strong impairment in olfactory memory.

The Ca^{2+} permeability of AMPARs was increased both in mice with reduced normal GluRB subunit expression and in those expressing the mutant form, and the authors propose that this might account for their enhanced olfactory discrimination. The enhancement itself, they suggest, is the result of some alteration in olfactory information processing, not odour detection, because due to the spatial restriction of the genetic modification, GluRB subunit expression was not altered in the olfactory epithelium.

Olfactory memory, meanwhile, seems to be linked to the level of GluRB subunit expression in the forebrain, with lower levels correlating with increased memory impairment. Through restricted transgenic GluRB subunit expression, this effect on olfactory memory was further localized to the piriform cortex and hippocampus.

These findings take us a step closer to understanding the neural control of olfactory behaviour using a well thought-out combination of techniques, which could be used to unravel the neural mechanisms underlying various behaviours in olfactory and other systems.

Sarah Archibald


Closing the gap

Signalling through electrical synapses that are formed by gap junctions between neurons is important in the development of the mammalian central nervous system. Neuronal gap junctions are abundant immediately after birth, but subsequently decrease in number and remain at a low level, being confined to specific subsets of neurons in adults. Writing in Nature Neuroscience, Harsha Arumugam and colleagues show that the maturation of glutamatergic transmission is responsible for gap junction uncoupling during development. These researchers studied gap junction coupling in slices of the paraventricular nucleus and the supraoptic nucleus of the rat hypothalamus, as well as in dissociated hypothalamic cultures, by using the coupling tracer neurobiotin, which passes through gap junctions. They found that the incidence of dye coupling increased during the first 2 weeks of postnatal development or in culture, and then declined significantly. These changes in gap junction coupling correlated with changes in the expression of connexin 36—a neuron-specific gap junction protein.

When the hypothalamic cultures were chronically treated with the NMDA (N-methyl-d-aspartate) receptor antagonist dizocilpine, developmental uncoupling of gap junctions and downregulation of connexin 36 were abolished—an effect that was mimicked in cultures by the voltage-gated sodium channel blocker tetrodotoxin, which attenuates action potentials.

Targeting neural correlates of addiction

Repeated exposure to drugs of abuse such as amphetamine, cocaine and nicotine can lead to long-lasting changes in the strength of synaptic transmission in mesocorticolimbic regions of the brain. Using new synthetic peptide inhibitors of a specific type of synaptic plasticity—the long-term depression (LTD) of excitatory neurotransmission—Brebner, Wong and colleagues identify molecular components of a neural adaptation that might underlie drug craving in addicts.

The drug-induced behavioural sensitization of motor activity—in which a long-lasting increase in the locomotor stimulatory effects of a drug of abuse is seen after repeated administration—is used to model some of the core features of addiction and the development of drug-induced psychosis. Changes in synaptic strength in the ventral tegmental area (VTA) are associated with the induction of behavioural sensitization, whereas synaptic plasticity in the nucleus accumbens (NAc), which receives dopaminergic projections from the VTA, seems to be responsible for its long-term expression.

In particular, enhanced LTD of glutamatergic transmission in the NAc has been identified as a neural correlate of behavioural sensitization to cocaine. Now Brebner et al. take an important step further by providing insights into the molecular mechanisms that underlie NAc LTD and the expression of behavioural sensitization to amphetamine.

To find out whether facilitated endocytosis of postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors contributes to LTD in the NAc, as it does in the hippocampus, the
Arumugam and co-workers next set out to determine the signal transduction pathways involved in downregulation of connexin 36 expression and uncoupling of neuronal gap junctions during development. They found that gap junction coupling and connexin 36 expression did not decrease in hypothalamic cultures treated with either an inhibitor of the calcium/calcmodulin-dependent protein kinases II and IV (CaMKII/IV) or a blocker of protein kinase C (PKC).

In addition, overexpression of the calcium–cyclic AMP responsive element-binding protein (CREB), which is found downstream of the CaMKII/IV and PKC pathways, accelerated the decrease in connexin 36 expression and gap junction uncoupling in culture, whereas overexpression of a dominant-negative mutant form of CREB had the opposite effect. Consistent with a role for CREB in NMDA-mediated effects, application of NMDA to hypothalamic cultures increased the amount of phospho-CREB, and this effect could be blocked by inhibitors of CaMKII/IV and PKC.

The researchers conclude that NMDA receptor-mediated glutamatergic transmission and action potentials are important for regulating developmental gap junction uncoupling and decreases in connexin 36 expression. This makes sense, as neuronal gap junction uncoupling occurs during the first 3 weeks of postnatal development, which is also the main period of which chemical synapse formation and increased synaptic activity.

Jane Qiu

The researchers then used a membrane-permeant form of GluR2 peptide to target NAc LTD in freely moving rats. The peptide blocked the expression of amphetamine-induced behavioural sensitization, raising the interesting question of whether GluR2-dependent AMPA receptor endocytosis is involved in the intensification of drug craving seen in human addicts with repeated drug exposure.

This study highlights the value of peptides that specifically disrupt the final step in the expression of synaptic plasticity in studying the neural correlates of behavioural sensitization. The researchers propose that such peptides could also provide a basis for the development of drugs to treat the maladaptive neural adaptations associated with drug addiction.

Rebecca Craven

The IκB kinase complex IκK is a central component of the signalling cascade that controls nuclear factor-κB-dependent gene transcription. Its function in the brain is largely unknown. Herrmann et al. show that IκK is activated in a mouse model of stroke. Constitutive activation of IκK increases the infarct size, whereas interference with IκK function in neurons reduces ischaemic brain damage. A small-molecule inhibitor of IκK can mimic this effect, which indicates that this class of IκK inhibitors could provide a new neuroprotective strategy.

Jane Qiu

AQP4 in astroglia migration and glial scar formation.

Saadoun, S. et al. J. Cell Sci. 22 November 2005 (10.1242/jcs.02680) Aquaporin 4 (AQP4), the main water-selective channel in astroglia throughout the CNS, facilitates water movement into and out of the brain. The authors report a novel role for AQP4 in astroglia migration and glial scar formation. Astroglia cultured from the neocortex of AQP4-knockout mice had normal morphology as well as proliferative and adhesive activity, but their migratory ability was markedly impaired. In AQP4-knockout mice, glial scar formation was significantly attenuated, with reduced migration of reactive astroglia towards the site of injury.


IκK mediates ischemia-induced neuronal death.

Herrmann, O. et al. Nature Med. 15 November 2005 (10.1038/nm1323) The IκB kinase complex IκK is a central component of the signalling cascade that controls nuclear factor-κB-dependent gene transcription. Its function in the brain is largely unknown. Herrmann et al. show that IκK is activated in a mouse model of stroke. Constitutive activation of IκK increases the infarct size, whereas interference with IκK function in neurons reduces ischaemic brain damage. A small-molecule inhibitor of IκK can mimic this effect, which indicates that this class of IκK inhibitors could provide a new neuroprotective strategy.

IN BRIEF

NEUROLOGICAL DISORDERS

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CELL BIOLOGY OF THE NEURON

The cell cycle–apoptosis connection revisited in the adult brain.

Bauer, S. & Patterson, P. H. J. Cell Biol. 171, 641–650 (2005) Adult neurogenesis is studied using thymidine analogues such as bromodeoxyuridine (BrdU) to label DNA synthesis. However, it is not clear whether BrdU also labels DNA synthesis events not directly related to cell proliferation, such as DNA repair and/or abortive re-entry into the cell cycle, which can occur as part of an apoptotic process in postmitotic neurons. Using three well-characterized models of injury-induced neuronal apoptosis, Bauer and Patterson found that BrdU is not significantly incorporated during DNA repair and that labelling is undetectable in dying postmitotic neurons.

GLIA

Involvement of aquaporin-4 in astroglial cell migration and glial scar formation.

Saadoun, S. et al. J. Cell Sci. 22 November 2005 (10.1242/jcs.02680) Aquaporin 4 (AQP4), the main water-selective channel in astroglia throughout the CNS, facilitates water movement into and out of the brain. The authors report a novel role for AQP4 in astroglia migration and glial scar formation. Astroglia cultured from the neocortex of AQP4-knockout mice had normal morphology as well as proliferative and adhesive activity, but their migratory ability was markedly impaired. In AQP4-knockout mice, glial scar formation was significantly attenuated, with reduced migration of reactive astroglia towards the site of injury.

COGNITIVE NEUROSCIENCE

DCDC2 is associated with reading disability and modulates neuronal development in the brain.

Meng, H. et al. Proc. Natl Acad. Sci. USA 22 November 2005 (10.1073/pnas.0508591102) The DYX2 on chromosome 6p22, which contains ~19 genes, is the most replicated reading disability locus. Meng et al. have identified a large polymorphic deletion of DCDC2, which lies on this locus, in families with reading disabilities. DCDC2 localizes to regions of the human brain responsible for fluent reading, and interference of DCDC2 expression in rat embryos causes defects in neuronal migration during development. The authors propose that DCDC2 is a candidate gene for reading disabilities.