gyrus, but also suggest roles for SDF1–CXCR4 in adult plasticity (learning and memory) and possibly in developmental disorders in humans that involve hippocampal pathology. Recent studies have shown that injury to the nervous system can trigger the migration of neural stem cells and newly generated neurons to the site of injury, and it will be of considerable interest to determine the role of SDF1 in this regenerative process. Finally, an increasing number of neurological disorders that involve defects in cell migration are being identified, and a better understanding of the signaling mechanisms that regulate such morphogenic processes in the developing and adult nervous systems could reveal novel approaches for preventing and treating these disorders.

1 Bagri, A. *et al.* (2002) The chemokine SDF1 regulates migration of dentate granule neurons. *Development* 129, 4249–4260

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A new NMDA-receptor blocker provides potential neuroprotection

Glutamate neurotoxicity is implicated in the pathogenesis of neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's diseases, and also plays a role in brain damage caused by head trauma, stroke and brain-tumour progression.

NMDA-receptor channels are very permeable to Ca^{2+}. Glutamate-mediated Ca^{2+} influx into neurons sets up a glutamate–nitric oxide–cGMP pathway, which eventually results in cell death by necrosis or apoptosis. Therefore, drug development aimed at neuroprotection has targeted the NMDA receptor. Unfortunately, at present, NMDA-receptor antagonists have serious cognitive side effects that interfere with their therapeutic benefit. These antagonists have strong affinity, and bind not only to pathologically active receptors, but also to physiologically active receptor sites, thereby interfering with the normal processes of memory and learning. Non-competitive channel blockers bind preferentially to pathologically active receptors. A potential neuroprotectant non-competitive NMDA-channel blocker would need the attributes of low molecular weight, low receptor affinity and fast on–off kinetics.

Planells-Cases *et al.* screened a restricted oligo-*N*-substituted glycine-based combinatorial library to find novel antagonists of the NMDA receptor [1].

'N20C is a non-competitive blocker that binds to the same non-competitive site as MK801, deep in the NMDA-receptor channel pore, thereby interfering with Ca^{2+} permeability.'

The rationale for this was the finding that arginine-rich hexapeptides blocked NMDA receptors with high efficacy and exhibited neuroprotectant activity *in vitro*. However, *in vivo*, the compounds were toxic at therapeutic doses. The library identified trimers of *N*-alkylglycine with a 3,3-diphenylpropyl amino moeity that blocked NMDA-receptor channels. Structure–activity relationships demonstrated that one compound, N20C, selectively inhibited NMDA receptors with micromolar affinity, and had fast on–off kinetics and strong voltage dependence. It did not compete for binding with glycine or glutamate, but prevented high affinity MK801 binding. The authors concluded, therefore, that N20C is a non-competitive blocker that binds to the same non-competitive site as MK801, deep in the NMDA-receptor channel pore, thereby interfering with Ca^{2+} permeability. *In vitro* and *in vivo* experiments also demonstrated that N20C has a neuroprotectant effect on glutamate-induced neuronal cell death.

The extent of neuroprotection provided by N20C was shown to be higher than that of memantine, and a better therapeutic profile was also suggested. The compound did not exhibit toxicity at high concentrations, and animals treated with *N*-alkylglycine did not display any conspicuous behavioural or motor deficits. Although the authors caution that a therapeutic index needs to be determined for this new open-channel blocker, this study represents an exciting step in the discovery of a neuroprotectant drug that has the potential to treat many neurodegenerative diseases.

1 Planells-Cases, R. *et al.* (2002) A novel N-methyl-D-aspartate receptor open channel blocker with *in vivo* neuroprotectant activity. *J. Pharmacol. Exp. Ther.* 302, 163–173

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Molecular neuropaleontology: resurrecting dinosaur vision

Dinosaur physiology has long fascinated scientists, but current debates about the validity of hypotheses concerning the metabolic rates and lifestyles of these long-extinct animals are often fuelled by speculations based on fossil evidence. Dinosaur neurophysiology, in particular, appears to be forever condemned to this speculative realm, because fossils that preserve information on dynamic physiological functions are extremely rare. How can one elucidate physiological functions in the absence of living specimens of these extinct creatures? One way to 'resurrect' bits and pieces of enticing insights into the neurophysiology of dinosaurs is to try to recreate specific molecules that have been conserved across evolution and that are believed to closely resemble molecules that existed during the time of the dinosaurs. Ancestral genes from ancient organisms, and the proteins encoded by them, can be reconstructed *de novo* and tested for function by using phylogenetic and biochemical methods. A recent study by Chang *et al.* [1] reports an exciting development in the field of molecular evolution: these investigators have succeeded in recreating a functional ancestral visual pigment believed to have existed in ancestors of archosaurs, animals that gave rise to some of the largest dinosaurs to walk the earth, including late Cretaceous carnivores.

Visual pigments are essential for triggering the cascade of microchemical reactions that enable organisms to see the world around them. Rhodopsin is one such pigment that is crucial for vision at low levels of ambient light. Chang *et al.* used maximum-likelihood reconstruction methods to construct models that guided their re-creation of an ancestral archosaur rhodopsin. Thirty vertebrate rhodopsin nucleotide sequences were used to reconstruct the archosaur rhodopsin, based on current understanding of systematic relationships among several vertebrate lineages. Maximum-likelihood models were generated to provide an overall best fit of the amino acid sequence of the ancestral archosaur protein to the sequences of these vertebrate rhodopsins. Chang *et al.* then used the artificially reconstructed archosaur rhodopsin amino sequence to design an artificial gene, which was produced on an oligonucleotide synthesizer. This gene was transfected into monkey kidney cells, and the rhodopsin was purified and its function tested. This reconstructed rhodopsin was shown to bind to 11-*cis* retinal (another protein needed for phototransduction) to produce a stable pigment with an absorption maximum at 508 nm, which is within the range of values reported for reptiles and birds. Additionally, the archosaurian rhodopsin was activated by transducin, a G-protein essential for phototransduction. Activation occurred at a rate similar to that of bovine rhodopsin. Alternative versions of the reconstructed rhodopsin were also tested for phototransduction, and they all showed similar spectral properties and transducin-activation rates.

'Thus, a valuable piece of information about the sensory capabilities of a long-extinct group of animals can be obtained from the application of phylogenetic methods to infer ancestral sequences of genes and proteins.'

These results suggest that archosaurs, long-extinct ancestors of dinosaurs, might have used a class of visual pigments that enabled visual competence under dim-light conditions. Thus, a valuable piece of information about the sensory capabilities of a long-extinct group of animals can be obtained from the application of phylogenetic methods to infer ancestral sequences of genes and proteins.

This elegant study reveals that, although it is impossible to define unambiguously the details of dinosaur physiology, a comparative phylogenetic approach, using molecular data from extant species that are believed to be descendants of dinosaurs, can still provide stimulating data on the physiological properties of molecules that probably existed and functioned millions of years ago during the Triassic period.

1 Chang, B.W. *et al.* (2002). Recreating a functional ancestral archosaur visual pigment. *Mol. Biol. Evol.* 19, 1483–1489

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In Brief

Emotions handicap focus

In the brain, attention-requiring tasks and emotions move in parallel circuits before finally converging. The two streams are integrated in a region of the brain known as the anterior cingulate gyrus, which is involved in a wide range of thought processes and emotional responses.

When test subjects were recently asked to pay attention to specific visual targets, researchers confirmed previous indications that emotional stimuli are likely to cause a person to lose focus. By using functional MRI, the study shows that emotional processing tends to occur in the ventral, or lower, part of the prefrontal cortex, whereas attentional tasks occur near the top. Surprisingly, an increase in one type of function is accompanied by a noticeable decrease in the other. This could explain why we lose focus when we surrender to our emotions. These results also present new avenues of research for treating depression, attention-deficit disorder, post-traumatic stress syndrome and Alzheimer's disease, which share the common feature of engaging the prefrontal cortex. (*Proc. Natl. Acad. Sci. U. S. A.* 99, 11447–11451)

Abnormal lipid metabolism in Lou Gehrig's Disease

Novel experiments indicate that exposure of mouse motoneurons to free radicals, reactive molecules with unpaired electrons, impairs their lipid metabolism, indicating that free radicals are involved in the onset and progression of amyotrophic lateral sclerosis (ALS).

ALS, also known as Lou Gehrig's disease, is a progressive and fatal neurological disease in which motoneurons gradually degenerate, causing muscle wasting and paralysis. As a result, a normally functioning mind is trapped inside a paralyzed body. Previous studies have shown that levels of ceramides and cholesterol are significantly higher in the spinal cord of people with ALS, as well as in animal models of ALS. The Cu^{2+}–Zn^{2+}-superoxide dismutase (Cu/Zn-SOD) is an important intracellular free radical scavenger. Mice deficient in this enzyme suffer from progressive motoneuron degeneration, just as in human ALS. Interestingly, levels of ceramides and cholesterol increase in cells exposed to oxidative stress, just as was found in motoneurons affected by ALS. The drug ISP-1 prevents the formation of precursor sphingolipids, which, in turn, produce ceramides. When exposed to oxygen free radicals, motoneurons treated with ISP-1 did not accumulate ceramides and cholesterol esters, nor did they degenerate.

This result indicates that ceramide accumulation is both necessary and sufficient to explain the degeneration of spinal cord motoneurons in ALS. Whether changes in dietary intake of cholesterol and lipids involved in the formation of membrane sphingolipids could affect the susceptibility of an individual to ALS is yet to be determined. (*Ann. Neurol.* 52, 22 Aug 2002, DOI 10.1002/ana.10312)

Anti-psychotic used to ameliorate autistic behavior

A new drug called Risperidone could be useful in treating severe behavioral problems associated with autism in children. Risperidone is an anti-psychotic

