IN THE NEWS

From stem cells to neurons?

Reactions in the press last month were uncharacteristically subdued when Ole Isacson and colleagues announced in *Proceedings of the National Academy of Sciences* that embryonic mouse stem cells, implanted into the striatum of a rat model of Parkinson's disease, could turn into functional dopaminergic neurons. They found that in more than 60% of implanted rats, the stem cells not only developed a dopaminergic phenotype, but also reduced motor asymmetry and normalized corticostriatal responses, as measured by functional imaging.

All of the news stories led with a positive angle. Many, including one in *USA Today* (7 January 2002), quoted Isacson as saying, "if further experiments are successful, there could be human trials of the technique in about five years." But although hopes will have been raised among patients and their families by some of the headlines, the media responsibly presented the problems as well as the promise of this potential new treatment. All of the stories focused on a problem with the study — the fact that 20% of rats that received the transplants developed teratomas.

The online *BBC News* site (8 January 2002) carried perhaps the most critical story, including quotes from an interview with UK researcher Roger Barker. He suggested that it might be possible to engineer stem cells with a 'suicide gene' that could be turned on if a teratoma developed. But he also said, "I don't think this will be a treatment in humans for quite some time", which will certainly have dampened some of the raised expectations.

Rachel Jones

MOTOR CONTROL

Keeping in step

The forelimbs and hindlimbs of quadrupeds must be coordinated with each other during locomotion. In humans, however, it is less clear to what extent the arms and legs are coordinated during walking, or where in the nervous system this coordination might occur. Two recent papers have have used different approaches to investigate the coordination of arm and leg movements in humans.

In the first of these studies, Dietz *et al.* investigated whether humans show interlimb coordination similar to that found in quadrupeds, in which propriospinal reflex circuits help to coordinate the forelimbs and hindlimbs. While people were walking on a split treadmill, the authors displaced the right leg slightly by causing the right side of the treadmill to speed up or slow down briefly. Recordings from the leg and arm muscles showed that this kind of displacement caused a stereotyped pattern of electromyographic responses in the left leg — which would be expected, to compensate for the unexpected displacement of the right leg — and in both arms. Stimulating the tibial nerve, which innervates the lower leg, caused a similar response.

By contrast, when the subjects were standing still or sitting down, leg displacement or tibial nerve stimulation caused little or no response of the arm muscles. These data support the idea that humans have a flexible neuronal coupling between leg and arm muscles that can be turned on or off depending on the task, and which coordinates the movement of the legs and arms during walking. The authors suggest that the proximal arm muscles are associated with the swinging of the arms during walking, and that this movement reflects our evolutionary origins as quadrupeds.

The second study, by Debaere *et al.*, used functional magnetic resonance imaging (fMRI) to look at the control of interlimb coordination by the brain. They asked people to perform a task that involved circling their wrists and ankles either in the same direction or in opposite directions, while keeping time with a metronome. Then the

ION CHANNEL STRUCTURE

Histamine's comeback?

Histamine, a biogenic amine related to histidine, is best known for its role in allergic reactions, during which it is released by mast cells to cause vasodilation and the all-too-familiar runny nose. The fact that histamine also has an important function as a neurotransmitter is less well known. For example, cells in the visual system of *Drosophila* respond to histamine, and this molecule is regarded as one of the main transmitters in the eye of the fly. Unfortunately, we know very little about the receptor that mediates this effect of histamine, apart from the fact that it is an unidentified chloride channel. But now two papers report the discovery of two cDNAs from *Drosophila* that code for a pair of histamine-gated chloride channels that might just be the missing receptor.

As ligand-gated ion channels share several structural features, Gisselmann *et al.* searched the *Drosophila* genome for new members of this channel superfamily. They identified several sequences that could potentially encode ligand-gated channels, expressed them in *Xenopus* oocytes, and tested their sensitivity to histamine. This approach led the authors to discover two histamine-gated, chloride-permeable channels: DM-HisCl-α1 and -α2. The properties of these channels, especially those of DM-HisCl-α1, partly matched the known characteristics of the native *Drosophila* receptor. So, DM-HisCl-α1 (but not -α2) was present in the *Drosophila* eye, and the pharmacological profile of both recombinant channels was similar to that of the native channel. Using a related approach, Zheng *et al.* made similar observations and further provided evidence that the two proteins can assemble to form heteromeric channels.

Although so-called 'histaminergic' pathways have been described in the mammalian brain, they have not received as much experimental attention as other transmitter systems, partly because the tools available to study them have not allowed us to answer many challenging questions. Metabotropic histamine receptors have been identified in mammals, but it is now tempting to speculate that channels similar to those reported in these two papers might also exist in the mammalian brain. Their findings should certainly rekindle our interest in the role of histamine in mammalian neurotransmission.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPERS Gisselmann, G. *et al*. Two cDNAs coding for histamine-gated ion channels in *D. melanogaster*. *Nature Neurosci.* **5**, 11–12 (2002) | Zheng, Y. *et al*. Identification of two novel *Drosophila melanogaster* histamine-gated chloride channel subunits expressed in the eye. *J. Biol. Chem*. **277**, 2000-2005 (2002)

FURTHER READING Schwartz, J. C. *et al*. Histaminergic transmission in the mammalian brain. *Physiol. Rev.* **71**, 1–51 (1991)

authors compared the fMRI activation produced by these movements with the sum of the activations produced when subjects moved either the wrist alone or the ankle alone.

The task that required the coordination of wrist and ankle movements caused increased activation in a network of brain areas, including the supplementary motor area, cingulate motor cortex, premotor cortex and cerebellum, indicating that this distributed network of motor areas is important for interlimb coordination. The authors then compared the two coordinated tasks — moving the wrist and ankle in the same direction or in opposite directions. Moving the two limbs in opposite directions is more difficult, and this was reflected in increased activation during this task. But, interestingly, the higher activation did not occur throughout the network — instead, it was limited to the supplementary motor area. This area has been implicated in bimanual coordination, but these new data provide evidence that it is also important for other types of limb coordination.

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Dietz, V. *et al.* Neuronal coordination of arm and leg movements during human locomotion. *Eur. J. Neurosci.* **14**, 1906–1914 (2001) | Debaere, P. *et al*. Brain areas involved in interlimb coordination: a distributed network. *Neuroimage* **14**, 947–958 (2001)

WEB SITES

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IN BRIEF

NEURODEGENERATIVE DISEASES

Recruitment and activation of caspase-8 by the Huntingtin-interacting protein Hip-1 and a novel partner Hippi.

Gervais, F. G. *et al*. *Nature Cell Biol.* 14 January 2002 (10.1038/ncb735)

It is not clear why expansion of the polyglutamine repeats in the protein huntingtin causes striatal neurons to die in Huntington's disease. Gervais *et al.* have cloned a new protein that might be important in this process. Normal huntingtin binds to another protein, Hip1, but expanded huntingtin binds less tightly, releasing Hip1 to interact with the newly identified protein, Hippi. The complex of Hip1 and Hippi can recruit procaspase 8 to activate an apoptotic pathway, which could lead to cell death.

SYNAPTIC PLASTICITY

Long-term potentiation and contextual fear conditioning increase neuronal glutamate uptake.

Levenson, J. *et al*. *Nature Neurosci.* 14 January 2002 (10.1038/nn791)

Glutamate transporters serve important functions at synaptic clefts, controlling the time course and concentration of glutamate after its release. Levenson *et al.* report that the induction of long-term potentiation (LTP) in area CA1 of the rat hippocampus causes an NMDA-receptor-dependent increase in glutamate uptake, and that LTP is also associated with translocation of the glutamate transporter from the cytosol to the membrane. An increase in glutamate uptake also occurred in rats during contextual fear conditioning, a hippocampus-dependent form of learning.

DEVELOPMENT

Opponent activities of Shh and BMP signaling during floor plate induction *in vivo*.

Patten, I. & Placzek, M. *Curr. Biol.* **12**, 47–52 (2002)

Induction of the floor plate during vertebrate development depends on the secreted molecule sonic hedgehog (Shh), but Patten and Placzek now show that exogenous Shh alone cannot induce an ectopic floor plate in the embryonic chick neural tube *in vivo*. However, when Shh was applied with chordin, an antagonist of bone morphogenetic protein (BMP) that is normally expressed in the notochord, a floor plate was induced. It is proposed that dorsally derived BMPs can affect even the most ventral parts of the neural plate, unless they are antagonized by notochord-derived signals.

CIRCADIAN RHYTHMS

Posttranslational mechanisms regulate the mammalian circadian clock.

Lee, C. *et al*. *Cell* **107**, 855–867 (2001)

The authors find that the mouse circadian clock seems to be regulated by robust post-translational mechanisms. Per1, Per2, Clock and Bmal1 undergo circadian changes in phosphorylation, and these, together with patterns of protein abundance, subcellular localization and protein interactions, seem to be crucial for maintenance of the circadian clock.