suggesting that DAT has a greater role than SERT in cocaine reward/reinforcement in wild-type mice.

We lack a truly effective agent to block the rewarding and reinforcing effects of cocaine. These results indicate that therapeutic strategies targeting both dopamine- and serotonin-mediated pathways might be effective in combating cocaine addiction. Indeed, if the relationship in mice between transporter expression and reward is paralleled in humans, a drug causing strong inhibition of cocaine binding to DAT and moderate inhibition of binding to SERT while sparing transmitter reuptake might be highly efficacious. Alternatively, drugs targeting specific dopamine and serotonin receptors could prove to be a rewarding avenue of research.

Peter Kirkpatrick, Associate Editor, Nature Reviews Drug Discovery

References and links

ORIGINAL RESEARCH PAPER Sora, I. *et al.* Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *Proc. Natl Acad. Sci. USA* **98**, 5300–5305 (2001)

FURTHER READING Nestler, E. J. Molecular basis of long-term plasticity underlying addiction. *Nature Rev. Neurosci.* **2**, 119–128 (2001)

during development, and their axons establish new commissural paths instead of extending into pre-existing trajectories. Lorent *et al.* propose that the product of the *space cadet* gene is required for the formation of late-developing commissures and could have a role in pioneering new axonal trajectories.

So, Lorent *et al.* have shown that the spiral fibre neurons are an important component of the motor circuit that underlies fast turning movements in zebrafish. They also provide a rare example of a single gene mutation that profoundly affects a specific motor response, and it will be very interesting to find out what type of factor is encoded by the *space cadet* gene.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Lorent, K. *et al.* The zebrafish *space cadet* gene controls axonal pathfinding of neurons that modulate fast turning movements. *Development* **128**, 2131–2142 (2001)

FURTHER READING Granato, M. & Nusslein-Volhard, C. Fishing for genes controlling development. *Curr. Opin. Genet. Dev.* **6**, 461–468 (1996)

SYNAPTIC PHYSIOLOGY

Getting up to speed on release

Information processing in the central nervous system depends, to a large extent, on the rate at which signals are transmitted at chemical synapses. For signals to be conveyed faithfully from presynaptic to postsynaptic neuron, every action potential arriving at the presynaptic terminal should elicit the release of neurotransmitter — to maintain synaptic transmission during periods of high-frequency firing (of up to several hundred action potentials per second), the presynaptic neuron should be capable of transmitter release at a similarly high rate. The maximum possible rate of release will depend, among other things, on the number of presynaptic release sites (active zones) and the rate at which synaptic vesicles can fuse with the cell membrane.

So, how fast can a conventional synapse release transmitter from vesicular stores? Previous estimates have been surprisingly low, at around 20 vesicles per second per release site; too slow, in fact, to follow the high-frequency firing observed at many central synapses. One possible explanation for this lies in the method used to determine the rate of transmitter release. By monitoring postsynaptic responses as a proxy for presynaptic exocytosis, a number of factors could have led to underestimates of the rate of release; for example, the saturation or desensitization of postsynaptic receptors. A more direct measure of the number of vesicles fusing with the presynaptic membrane can be made at synapses where the nerve terminal is large; in this case, individual fusion events can be detected as an increase in the presynaptic membrane capacitance. Would this approach lead to higher estimates of the speed of release at central synapses?

To address this question, Sun and Wu studied glutamate release at one of the largest synapses in the rat brainstem — the calyx of Held. By recording from the large presynaptic terminal at this synapse, which fires at high frequency *in vivo*, they were able to make presynaptic capacitance measurements, while simultaneously monitoring the excitatory postsynaptic currents (EPSCs) arising from glutamate release. As they report in *Neuron*, Sun and Wu found that EPSC amplitudes were saturated when capacitance measurements had only reached 35% of their maximum value, supporting the prediction that measuring presynaptic vesicular fusion does indeed lead to higher estimates of the amount of transmitter released — more than 300 vesicles per second per active zone in the case of this preparation.

These findings show that conventional central synapses can liberate transmitter at a much higher rate than was previously estimated; high enough to match the rate of incoming action potentials during periods of high-frequency stimulation. The ability to monitor synaptic transmission simultaneously from both the presynaptic terminal and the postsynaptic neuron at the calyx of Held provides a means of learning more about the features of transmitter release at a central site.

Rebecca Craven

References and links

ORIGINAL RESEARCH PAPER Sun, J.-Y. & Wu, L.-G. Fast kinetics of exocytosis revealed by simultaneous measurements of presynaptic capacitance and postsynaptic currents at a central synapse. *Neuron* **30**, 171–182 (2001)

FURTHER READING Bollmann, J. H., Sakmann, B. & Borst, J. G. Calcium sensitivity of glutamate release in a calyx-type terminal. *Science* **289**, 953–957 (2000) | Schneggenburger, R. & Neher, E. Intracellular calcium dependence of transmitter release rates at a fast central synapse. *Nature* **406**, 889–893 (2000)

GENE THERAPY

Infectious neuroscience

The honeymoon period is nearly over for the use of recombinant adeno-associated viruses (rAAVs) in neurobiology. It's time for this approach to start living up to the expectations that it generated and, indeed, a recent report in *Nature Genetics* reassures us about the potential of rAAVs for gene therapy. Using a genetic model of childhood blindness, Acland *et al.* have shown that the rAAV-mediated transfer of *RPE65*, a gene expressed by the retinal pigment epithelium, prevents retinal degeneration in dogs.

Mutations in *RPE65* in humans lead to a severe form of retinal degeneration — Leber congenital amaurosis. *RPE65* mutations in dogs have a similar effect and the authors used this model to test the effect of subretinal injections of an rAAV–*RPE65* construct. They found that retinal degeneration was in fact reduced; electroretinographic recordings in the injected animals resembled those in wild-type dogs and behavioural experiments showed that vision was restored. This is the first report of successful gene therapy to prevent blindness in a large mammal and it should stimulate further research into the usefulness of the approach in humans.

But as rAAVs begin to fulfil their promise, new viral vectors are starting to appear. The latest newcomer is a pseudorabies virus (PRV) that, as reported in *Science*, replicates only in neurons that express Cre recombinase. As PRV has previously been used as a neuronal tracer, the development of this conditional vector and its use in combination with appropriate transgenic methods could allow greater specificity in anatomical studies.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Acland, G. M. *et al.* Gene therapy restores vision in a canine model of childhood blindness. *Nature Genet.* **28**, 92–95 (2001) | DeFalco, J. *et al.* Virus-assisted mapping of neural inputs to a feeding center in the hypothalamus. *Science* **291**, 2608–2613 (2001)

FURTHER READING Bennett, J. & Maguire, A. Gene therapy for ocular disease. *Mol. Ther.* **1**, 501–505 (2000)

© 2001 Macmillan Magazines Ltd