

## CLINICAL PERSPECTIVES

**Against addiction: light at the end of the tunnel?**

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Drug addiction is the among the most costly brain diseases, totaling 57 billion euros in direct and indirect costs in Europe alone. It is a disease without cure. Although it is impossible to say how far off we are from seeing the light at the end of the tunnel, substantial advances have been made over the last decade.

The emerging model that addiction is a disease of 'learning gone wrong' is now widely accepted (Redish *et al.* 2008). Of particular interest in this context is the observation that all addictive drugs, and only addictive drugs, drive specific forms of synaptic plasticity in the mesolimbic system. Sometimes also referred to as the reward system, the mesolimbic system originates in the ventral tegmental area and projects to the nucleus accumbens (NAc). In a paper in a recent issue of *The Journal of Physiology* D'Ascenzo *et al.* (2009) point to an interesting mechanism for how the excitability of neurons in the NAc is enhanced by type 5 metabotropic glutamate receptors (mGluR5). These receptors are distinct from the fast ionotropic AMPA and NMDA receptors, as they activate Gq-proteins and the enzyme phospholipase C. As a result, a calcium signalling pathway is engaged,

which recruits a sodium conductance that then changes the waveform of the action potential of these neurons. What might initially read like a story for specialists, suddenly becomes really exciting when the authors go on to show that this leads to an increase in the firing rates of neurons in the NAc.

The excitability of neurons of the NAc has been shown to change in association with several drug treatments. It is also thought to drive behaviours that mimic core components of addiction such as the preference for the environment where drugs have been administered or cue-induced drug seeking, which is a model for relapse. The seminal observation that the mutant mice lacking mGluR5 are insensitive to cocaine reward (Chiamulera *et al.* 2001) suggests that these receptors are involved in drug addiction.

However, the role of mGluR5s in the NAc, and therefore addiction, is likely to be more complex. In addition to enhancing the excitability of NAc neurons, they also drive the release of endocannabinoids. These lipophilic substances regulate, in turn, the amount of transmitter that is released by afferent neurons. The same mGluR5s also tap into the protein synthesis machinery to permanently change synaptic efficacy, a process referred to as protein synthesis-dependent synaptic plasticity.

Regardless of the admittedly complicated functions of the mGluR5s, one might ask whether mGluRs could be good therapeutic targets to treat drug addiction. In fact, several experimental compounds are available. A handful of reports suggest that mGluR5 antagonists might reduce symptoms of drug addiction when directly applied to the NAc. However, when given

systemically, mGluR5s are also inhibited elsewhere, which may have confounding effects. Moreover, mGluR1, a receptor of the same group of metabotropic receptors, seems to have the opposite effect. In fact, several studies suggest that mGluR1 enhancers may reverse cocaine-evoked synaptic plasticity (Mameli *et al.* 2007). These receptors therefore might have a protective role against addiction.

Even if mGluR5s drive neuron excitability as suggested here, this may not explain how behavioural changes come about. A very recent study using sophisticated opto-genetic tools concludes that the main effect depends on Gq signalling (Airan *et al.* 2009). The authors combined the light-sensitive rhodopsin with the cytoplasmic portion of G-protein coupled receptors and subsequently transfected this chimeric protein into neurons of the NAc using viral vectors. When they then used fibre optics to shine blue light on the neurons of the NAc in a freely moving mouse in order to excite the fusion protein, it was the activation of the Gq pathway rather than increased neuronal firing *per se* that appeared to drive the addiction-related behaviour.

These are, without doubt, exciting times and the (blue) light at the end of the tunnel may appear quicker than we think.

**References**

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