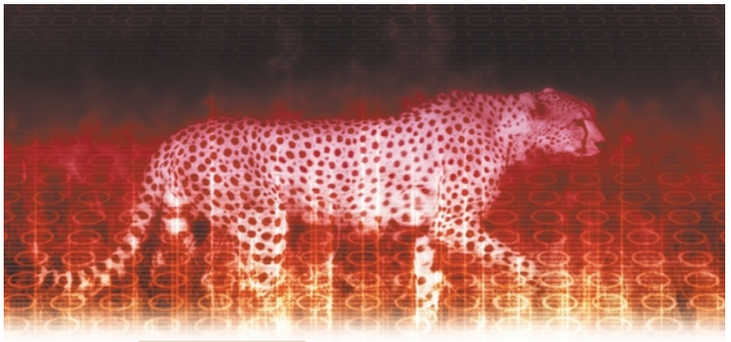

GAP JUNCTIONS

Closing the gap

Gap junctions, formed by the connexin family of proteins, span the membranes of and provide electrical continuity between adjacent cells. These channels allow the passage not only of ions, but also of molecules as large as second messengers. Most connexin channels have a voltage-sensitive gate, which closes when a voltage difference develops between cells. However, this closure is partial, and would not be expected to break the electrical continuity of the cells. So, what is the function of the voltage gate? In a recent report, Qu and Dahl provide some clues.

Gap junctions have at least two conductance states: the 'full conductance' state and a 'subconductance' state. Rather than closing completely, these channels spend longer periods of time in the subconductance state when the gate senses a voltage change. Qu and Dahl considered the possibility that channel selectivity in this state might differ from that in the full conductance state such that the passage of larger molecules would be reduced. In this way, the activated gate would allow electrical coupling, while obstructing the passage of metabolites and second messengers.

To test this idea, the authors expressed connexin 46 (Cx46) or Cx43 in *Xenopus* oocytes. They monitored the passage of fluorescent test molecules or cyclic AMP through Cx46 hemichannels expressed in single oocytes, and through full heterotypic (Cx46/Cx43) channels that formed between cells.

By recording from single Cx46 hemichannels, Qu and Dahl confirmed that the subconductance state predominates at positive holding potentials (+20 to +30 mV) compared with negative potentials (–30 to –20 mV). But when oocytes that expressed Cx46 were clamped at +20 mV (that is, when channels were induced to 'close'), the macroscopic membrane conductance was found to be higher than that recorded at –20 mV, presumably because there was an overall increase in the open time of the channel. However, the flux of fluorescent molecules or cAMP was greatly diminished by depolarization. Moreover, the flow of cAMP through Cx46/Cx43 channels was reduced when a voltage was applied across the junction. So, whereas the passage of small ions is largely undisturbed, the transit of larger molecules is reduced when the voltage gate is activated.

What is the physiological effect of this change in permeability? Qu and Dahl suggest that the gate might prevent the accumulation of charged molecules in parts of a tissue in the presence of an electrical field. As electrical synapses are present in many parts of the nervous system, this property of gap junctions might have a particularly important role in neuronal signalling.

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NEUROBIOLOGY OF ADDICTION

Leader of the pack

One of the most difficult questions facing researchers in drug abuse is why some people are more likely than others to become addicted to a drug. It seems likely that the difference is in some way due to brain chemistry, and in particular to variations in the dopaminergic system, which is thought to mediate reward, but exactly what these variations are and how they arise is unknown.

Of course, it is very difficult to study these questions in humans. A new study in monkeys might give us some clues about where to look. Morgan *et al.* carried out a long-term experiment in which they looked at the possible roles of dopaminergic function and social factors in vulnerability to drug abuse, and found that social dominance can influence both changes in dopaminergic function and self-administration of cocaine in monkeys.

First, the monkeys were studied while housed individually for a year and a half, and their brains were imaged using positron emission tomography (PET). Then they were put into social groups. After three months of living in these groups, the PET scans of the monkeys that had become dominant showed a significant increase in binding of a radioactive ligand, [^{18}F]fluoroclebopride (FCP), to dopaminergic receptors in the midbrain. This means that either there was an increase in the number of dopamine receptors or that there was a decrease in the amount of extracellular dopamine in the midbrains of these monkeys. Subordinate monkeys, by contrast, showed no changes in FCP binding.

These differences in dopaminergic function were associated with differences in cocaine self-administration rates. Subordinate monkeys reliably self-administered cocaine, but dominant monkeys did not, suggesting that they were resistant to the reinforcing effects of cocaine.

Several previous studies have indicated that social rank might relate to dopaminergic function and influence the effects of drugs, such as cocaine, in monkeys, but this is the first to show that becoming dominant after being individually housed can cause rapid changes in the midbrain dopaminergic system. If the differences in cocaine self-administration are the result of variations in the dopamine system, then they also result from differences in the social status of the monkeys.

Of course, it is a long way from this kind of model to human addicts. But greater understanding of the effects of social context on dopaminergic function and drug-related behaviour in monkeys could help us to understand whether similar forces affect the human dopaminergic system and influence the propensity of some people to become addicted, and could also provide a new model for testing methods of interfering with the reinforcing properties of addictive drugs.

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Michael Nader's lab: http://www.wfubmc.edu/physpharm/faculty/nader.html