ADDICTION

Identity of reward

Nicotine addiction is the largest cause of preventable mortality in the world and leads to more than 4 million smoking-related deaths every year. Until recently, it has been unclear which nicotinic receptors elicit the acute and chronic effects of nicotine dependence. Reporting in *Science*, Tapper and colleagues show that activation of α4 receptors is sufficient to mediate nicotine-induced reward, tolerance and sensitization.

Nicotine dependence begins with the binding of nicotine to nicotinic acetylcholine receptors (nAChRs) — pentameric cation-permeable ligand-gated ion channels that are normally activated by the endogenous neurotransmitter acetylcholine. At present, 12 nAChRs subunits have been identified, and many combinations can give rise to functional receptors. In this study, the authors generated 'knock-in' mice, in which the wild-type α4 subunit is replaced with one that contains a point mutation, leucine to alanine, within the putative pore-forming M2 domain and, as a result, is hypersensitive to nicotine.

They found that nicotine could induce calcium influx in cultured ventral midbrain neurons from mutant mice at a concentration that was 40-fold lower than for the wild-type cultures. Chronic administration of low doses of nicotine (50-fold lower than that found in the blood of smokers) resulted in a robust functional upregulation — an increase in the neuron's responsiveness to acetylcholine — in cultures from mutant but not wild-type mice. In addition, low concentrations of nicotine resulted in increased action potential firing frequency in the dopaminergic neurons from mutant mice, but had little effect on those from wild-type animals.

The mutant mice were also more prone to addiction-related effects at low concentrations of nicotine. In the 'conditioned place preference' test, mutant mice clearly preferred nicotine-paired boxes — an indication of a behavioural reinforcement response. Chronic administration of nicotine causes hypothermia, and tolerance to this effect is thought to be important in the development and maintenance of dependence. When single daily injections of nicotine were given at doses that induce hypothermia, only the mutant animals developed tolerance. Finally, repeated systemic injections of nicotine resulted in a steady increase in locomotor activity in mutant but not wild-type mice, which indicates that mutant animals became more sensitive to nicotine.

This elegant study not only provides direct evidence of which receptors promote nicotine dependence, but also raises fundamental questions about the genetics of addiction. Future work should shed light on whether polymorphisms in the human population could determine our susceptibility to addiction.

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References and links

ORIGINAL RESEARCH PAPER Tapper, A. R. *et al.* Nicotine activation of α4* receptors: sufficient for reward, tolerance, and sensitization. *Science* **306**, 1029–1032 (2004)

FURTHER READING Laviolette, S. R. & van der Kooy, D. The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. *Nature Rev. Neurosci.* **5**, 55–65 (2004)

WEB SITE Lester's laboratory: http://www.its.caltech.edu/~halweb/index.html

IN BRIEF

CELL BIOLOGY OF THE NEURON

Synaptobrevin is essential for fast synaptic-vesicle endocytosis.

Deák, F. *et al. Nature Cell Biol.* **6**, 1102–1108 (2004)

Synaptobrevin-2 (also known as VAMP-2) is a synaptic vesicle SNARE protein that is essential for fast, calcium-triggered exocytosis of synaptic vesicles. In this study, Deák and colleagues show that this protein is also required for fast endocytosis of vesicles at synapses, which is essential for normal vesicle recycling. In cultures of hippocampal neurons from mice that lack synaptobrevin-2, replenishment of the readily releasable pool of vesicles was significantly delayed, apparently owing to a defect in endocytosis. The fact that synaptobrevin is required for both fast exocytosis and fast endocytosis might reflect the functional coupling of these key processes, which allows vesicles to be rapidly reused during normal synaptic function.

BEHAVIOURAL NEUROSCIENCE

Hippocampal lesions disrupt navigation based on the shape of the environment.

McGregor, A. *et al. Behav. Neurosci.* **118**, 1011–1021 (2004)

The activity of 'place cells' in the CA1 region of the hippocampus is sensitive to an animal's position in space, and the hippocampus is thought to be important for spatial navigation. In this study, McGregor *et al.* show that excitotoxic lesions of the hippocampus prevent rats from being able to navigate to a goal (a hidden platform in a water maze) using shape information provided by physical barriers or landmarks. These findings support 'cognitive mapping' theories of hippocampal function, according to which the hippocampus helps to encode the relationships between an animal's location and enviromental cues.

SENSORY SYSTEMS

Early- and late-onset blind individuals show supra-normal auditory abilities in far-space.

Voss, P. *et al. Curr. Biol.* **14**, 1734–1738 (2004)

There is already evidence to show that blind individuals can surpass the performance of sighted people in tasks that require spatial hearing in the area immediately around the body, where auditory representations could be calibrated by sensory-motor feedback. The authors now show that this supra-normal performance extends to sound localization in more distant space. In addition, despite theories that these abilities rely on cross-modal reorganization of the cortex in subjects who are blind from birth or infancy, Voss and colleagues find that individuals who became blind later in life can also out-perform sighted people on tests of auditory localization. These results indicate that compensation can occur in adults as well as in children, perhaps through the activation of dormant horizontal connections between visual and auditory areas of cortex.