IN THE NEWS

Making sense of smell

Neuroscience is already well represented in the list of Nobel Prize laureates, and it was recently announced that the 2004 prize for physiology or medicine has been awarded to Linda Buck and Richard Axel for unlocking the secrets of what the Nobel Assembly described as "the most enigmatic of our senses" — the sense of smell.

Buck was a senior postdoctoral fellow in Axel's laboratory in 1991 when the pair published their seminal paper on the discovery of a family of around 1,000 'odorant receptor' genes. They subsequently became competitors in the race to establish how these receptors are deployed in the detection of over 10,000 different odours — a research effort that gave rise to the concept of a combinatorial olfactory code, which was described by Axel as "the brain…essentially saying something like 'I'm seeing activity in positions 1, 15, and 54 of the olfactory bulb, which corresponds to odorant receptors 1, 15, and 54, so that must be jasmine'" (*Times Online*, UK, 4 October).

As well as exposing the workings of the olfactory system, this research has contributed substantially to our understanding of the link between olfaction and memory: "how very specific smells — a great red wine, the scent of a lover or even an unfresh clam — can remain embedded in the human brain for years, only to be triggered half a lifetime later by a similar smell" (*Times Online*). This phenomenon was famously illustrated in "Marcel Proust's novel *Remembrance of Things Past*, where the smell and taste of a single madeleine cake triggers a long string of memories" (*Discovery Channel*, USA, 4 October).

When asked what he planned to do next, Axel said: "I'm going to have a cup of coffee" (*New York Times*, 4 October).

Heather Wood

NEUROLOGICAL DISORDERS

The calcium link of heart and mind

Autism affects 0.5% of children around the world and causes great distress, but little is known about the molecular mechanisms involved in this disorder and no therapy is yet available. Reporting in *Cell*, Splawski and colleagues implicate abnormal calcium signalling in autism, and highlight the therapeutic potential of calcium channel blockers.

The authors characterized the phenotypes and molecular basis of Timothy syndrome — a novel disorder that is associated with conditions in multiple organ systems, including lethal arrhythmias, immune deficiency and autism. They discovered a *de novo* missense mutation in a splice variant of the calcium L-type channel, $Ca_v1.2$, in 13 patients with the syndrome. The mutation, G406R, caused a substitution of glycine with arginine at residue 406.

This splice variant of $Ca_v1.2$ is expressed in many human adult and fetal tissues including the brain, gastrointestinal system, lungs, immune system, smooth muscle and testis — a pattern that is consistent with the phenotypic abnormalities associated with Timothy syndrome. In the brain, it is expressed in regions such as the hippocampus, cerebellum and amygdala where abnormalities have been implicated in autism.

Splawski and colleagues compared the biophysical properties of the wild-type and mutant $Ca_v1.2$, which were heterologously expressed in Chinese hamster ovary cells and *Xenopus laevis* oocytes. The G406R mutation completely abolishes voltage-dependent channel inactivation of $Ca_v1.2$ and results in persistence of inward Ca^{2+} currents in the cell. Computer simulation indicates that a prolonged Ca^{2+} current in cardiomyocytes might lengthen cardiac action potentials and delay repolarization, which would lead to an increased risk of arrhythmia. As the mutant $Ca_v1.2$ remains sensitive to calcium channel blockers such as dihydrophyridines, these drugs might be useful for treating Timothy syndrome and autism.

These findings hint at a potential mechanism that might underlie autism. Future studies will focus on the genetic analysis of $Ca_v1.2$ and other calcium channels in the disorder and the potential application of calcium channel blocker therapy.

Jane Qiu

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NEUROLOGICAL DISORDERS

Changes away from the synapse

According to a study published in the *Journal of Neuroscience*, changes to extrasynaptic GABA (γ-aminobutyric acid) receptors in a mouse model of epilepsy could contribute to overall changes in neural excitability.

Peng *et al.* studied the expression of specific GABA receptor subunits in mice in which epilepsy had been induced by treatment with pilocarpine. GABA receptors that contain the δ-subunit are usually found outside synapses, where they might be tonically active or activated by transmitter spillover from nearby synapses. These extrasynaptic GABA receptors are thought to be important for controlling neuronal excitability, and mutations in the gene for the δ-subunit have been identified in patients with generalized epilepsy.

In the mouse model of epilepsy that was used for this study, a single treatment with pilocarpine is used to induce a chronic epileptic condition with spontaneous seizures. The authors monitored changes in the expression of the δ-subunit over the period after the injection. After four days, diffuse immunohistochemical labelling for the δ-subunit was decreased in the molecular layer of the dentate gyrus, but after a week this general decrease in labelling was accompanied by a specific increase in the labelling of interneurons (most of which are inhibitory). These changes were sustained over the 60 days of the study.

If excitatory neurons in the dentate gyrus have fewer extrasynaptic GABA receptors, and inhibitory interneurons in the same area have more, this could lead to a decrease in overall inhibition in this area and an increase in the excitability of the neuronal network. To test this, the authors performed electrophysiology on brain slices from the pilocarpine-treated mice. As predicted, these slices were more excitable than those from control mice, and they were also resistant to the normal decrease in excitability caused by treatment with a neurosteroid.

These findings point to the potential importance of extrasynaptic GABA receptors in epilepsy, and show that differential changes in receptor expression in interneurons and principal neurons might produce a combined effect on excitability in models of epilepsy.

Rachel Jones

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