IN BRIEF

CHANNELS

The polar T1 interface is linked to conformational changes that open the voltage-gated potassium channel.

Minor, D. L. Jr *et al. Cell* **102**, 657–670 (2000).

The T1 domain of the Kv family of potassium channels is a cytoplasmic amino-terminal region involved in subunit tetramerization. Using a combination of crystallographic and thermodynamic methods, and through the mutational analysis of the Kv1.2 potassium channel, the authors show that residues located at the polar interface between T1 domains in different subunits participate in channel gating. Although the exact nature of the involvement of T1 has not been established, this finding should be taken into account for the development of new models of gating which, until now, have focused mostly on conformational shifts at the transmembrane segments of the channel.

SYNAPSES

Molecular memory by reversible translocation of calcium/calmodulin-dependent protein kinase II.

Shen, K. *et al. Nature Neurosci.* **3**, 881–886 (2000).

This paper shows that the transit of calcium/calmodulin-dependent kinase II (CaMKII) from the cytosol to the postsynaptic density elicited by glutamate receptor activation can modify the duration of a subsequent translocation event. Weak receptor stimulation in cultured neurons lead to a short-lasting translocation of CaMKII. Strong stimuli, in contrast, lead to a stable translocation that lasts for several minutes and requires the phosphorylation of Thr286. The reversibility of this process depends on the activity of protein phosphatase-1 and on the phosphorylation of Thr305/306. Following its dissociation from the postsynaptic density, CaMKII remains in a primed state such that a weak stimulus delivered soon after could now induce a more enduring translocation. These findings indicate that the function of CaMKII as a molecular switch for synaptic plasticity might not rest solely on its autophosphorylation capability, but that its function could also involve the 'memory' present in its translocation cycle.

MENTAL DISORDERS

A family-based and case control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder.

Holmes, J. *et al. Mol. Psychiat.* **5**, 523–530 (2000).

Attention deficit hyperactivity disorder is a psychiatric condition characterized by inattention, impulsiveness and excessive activity, and primarily affects children. This disorder seems to have a genetic component related to alterations in dopamine-mediated neurotransmission. This paper and three others in the same issue of the journal *Molecular Psychiatry* provide further support for this idea by finding different degrees of association between attention deficit hyperactivity disorder and certain alleles of the dopamine receptors 4 and 5 and of the serotonin receptors 2A and 1B.

SYNAPTIC PLASTICITY

Getting your kick from LTP

Molecules like nicotine, cocaine and morphine stimulate the release of dopamine in the nucleus accumbens — a major reward area of the brain. Not surprisingly, this stimulation seems to be related to the pleasurable feeling that accompanies the intake of these and other drugs of abuse, and to be responsible for their highly addictive nature. The main provider of dopamine to the nucleus accumbens is a mesencephalic nucleus known as the ventral tegmental area (VTA), and we know that, in the case of nicotine, its stimulatory effect is mediated by nicotinic acetylcholine receptors (nAChR) present on the somata of VTA neurons. An unresolved enigma, however, is the fact that although the rewarding effect of nicotine can last for a long time, nAChR desensitize very quickly. Mansvelder and McGehee have put a big piece of this puzzle into place by showing that nicotine not only acts directly on VTA neurons, but that it can also induce a long-lasting potentiation of the excitatory inputs to this nucleus.

Instead of focusing on the dopamine connections of the VTA cells onto the nucleus accumbens, Mansvelder and McGehee decided to investigate the effect of nicotine on the glutamate synapses received by the VTA from structures such as the prefrontal cortex. They observed that, in the absence of any other manipulation, a brief application of nicotine increased the amplitude of the excitatory synaptic currents through a presynaptic mechanism. This effect was short-lived and had previously been found in other brain regions. However, if they applied nicotine and depolarized the VTA neurons simultaneously, the potentiation of the currents showed an uncanny resemblance to long-term potentiation (LTP) in the CA1 region of the hippocampus — it lasted for long periods, it was sensitive to the presence of *N*-methyl-D-aspartate receptor antagonists, and it required the depolarization of the postsynaptic neuron.

The glutamate input to the VTA is known to influence the nicotine-induced enhancement of dopamine release in the nucleus accumbens, and it is likely that the potentiation unveiled by Mansvelder and McGehee plays a role in this phenomenon. It will be of interest to determine whether there is a behavioural correlate of this form of plasticity by testing, for instance, if nicotine self-administration actually depends on the induction of the potentiation. More importantly, one might wonder whether a similar potentiation is observed with other drugs of abuse such as heroin, which also increases dopamine release in the reward areas of the brain but is much more addictive. Clearly, those already addicted to the study of LTP will now find it even harder to kick the habit.

Juan Carlos López

Photograph courtesy of John S. Thompson, University of Chicago, Illinois, USA.

References and links

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