ION CHANNELS

In search of the 'mystery messenger'

After more than two decades of study, a key component of the signalling pathway that couples muscarinic receptor activation to modulation of the so-called M current (I_M) has been uncovered. In a paper published in *Neuron*, Suh and Hille present strong evidence that the consumption of phosphatidylinositol-4,5-bisphosphate (PIP_2) is central to M channel regulation.

I_M is a voltage-dependent K^+ current that is found in a range of neuronal cell types. Because the channels that carry this current — KCNQ channels — are active at the resting membrane potential, their inhibition leads to membrane depolarization. Since Brown and Adams first reported that muscarinic receptor agonists depress this current, a variety of agonists has been shown to modulate I_M . These agents exert their effects by binding to G-protein-coupled receptors; the subsequent suppression of I_M depends on the activation of $G_{q/11}$ and involves a diffusible signal. But the identity

of this 'mystery messenger' has remained an enigma.

As previous attempts to identify the mystery signal had failed to deliver, Suh and Hille opted for a new approach. Rather than focusing on the suppression of I_M , they examined the recovery of I_M after agonist removal. They showed that hydrolysable ATP is required for the restoration of the KCNQ2/KCNQ3 current after muscarinic suppression, and that phosphoinositide 4-kinase (PI4K) is essential for this ATP-dependent recovery. In addition, they confirmed that the induction of I_M inhibition is dependent on phospholipase C (PLC), a downstream effector of $G_{q/11}$.

So, the breakdown of PIP_2 by PLC, and its resynthesis by PI4K, seem to be central to I_M suppression and recovery, respectively. Although the identity of the diffusible second messenger has yet to be established, these findings provide some clear candidates for future research.

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LEARNING AND MEMORY

Weeding out memory extinction

Extinction is the reduction of a learned behavioural response on repeated presentations of a conditioned stimulus in the absence of a reinforcer. So, if we train a mouse to fear a tone that is paired with an electric shock, the mouse will freeze the next time it hears the tone, expecting to receive another shock. But if we continue to present the tone in the absence of shock, the association between the two stimuli will gradually become weaker, and the mouse will stop freezing. What are the neural bases of extinction? Reporting in *Nature*, Marsicano *et al.* provide evidence that endocannabinoids are crucially involved. As the extinction of aversive memories might be affected in states such as post-traumatic stress disorder and in certain phobias, the results point to the endocannabinoid system as a possible target for the treatment of these conditions.

Marsicano *et al.* generated mice that lacked the cannabinoid receptor CB1 and trained them in the aversive task that I have just described. CB1^{-/-} mice learned to freeze in response to the tone; however, in contrast to wild-type mice, the CB1-deficient animals failed to extinguish this behavioural response. Moreover, the CB1

antagonist SR141716A had the same effect on extinction if it was administered immediately before the tone.

The amygdala is key to learning the tone-shock association. Marsicano *et al.* therefore predicted that the levels of endogenous cannabinoids should rise in this brain structure immediately after presentation of the tone. Indeed, they confirmed this prediction for two endocannabinoids — anandamide and 2-arachidonoylglycerol. But how might these molecules affect synaptic transmission in the amygdala during extinction? We don't yet know, but the authors made an intriguing finding. In wild-type animals, low-frequency stimulation of inhibitory synapses in the amygdala led to a persistent depression of their efficacy. By contrast, this effect was missing in the amygdala of CB1^{-/-} mice or in the presence of SR141716A. So, endocannabinoids seem to participate in this synaptic depression, and it will now be important to determine whether and how this effect is related to extinction.

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