SYNAPTIC PLASTICITY

A new partnership

The endocannabinoid anandamide inhibits neurotransmitter release through presynaptic cannabinoid receptor 1 (CB1) receptors. Anandamide also binds transient receptor potential vanilloid 1 (TRPV1), but the physiological relevance of this binding has not been established. In addition, although the nociceptive role of TRPV1 on peripheral sensory neurons is well known, the function of this receptor in the brain is unclear. Now, two papers address both of these questions by showing that activation of central TRPV1 receptors by anandamide plays a key part in a postsynaptic form of long-term depression (LTD) in distinct brain regions.

Chavez *et al.* focused on excitatory synapses between medial perforant path neurons and dentate granule cells in the hippocampal formation. LTD induced at these synapses was blocked by application of TRPV1 antagonists in rodent slice preparations and was absent in slices from *Trpv1*$^{-/-}$ mice, indicating that LTD is TRPV1 dependent.

Next, the authors studied the involvement of metabotropic glutamate receptors (mGluRs) in this effect, as these are known to activate TRPV1 via phospholipase C (PLC). Inhibiting mGluR5 or PLC, but not mGluR1, blocked the induction of TRPV1-dependent LTD. Postsynaptic Ca^{2+} also seems to be involved in TRPV1-dependent LTD, as LTD was abolished by chelating intracellular Ca^{2+}, by blocking L-type Ca^{2+} channels or by depleting intracellular Ca^{2+} stores. In addition, inhibitors of calcineurin or dynamin — two Ca^{2+}-dependent proteins that facilitate endocytosis of AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors) — prevented LTD. The authors therefore proposed that elevated Ca^{2+} levels might cause LTD by increasing AMPAR internalization.

Anandamide is released following intracellular Ca^{2+} increases. Blocking anandamide degradation led to robust LTD in a subthreshold induction protocol in slices from wild-type mice but not *Trpv1*$^{-/-}$ mice, indicating that endogenous anandamide can induce TRPV1-dependent LTD.

Grueter *et al.* studied indirect pathway GABA (γ-aminobutyric acid)-ergic medium spiny neurons in slice preparations of the mouse nucleus accumbens (NAc) — a key region for reward-dependent learning and addiction. They found a similar mechanism of LTD that was dependent on mGluR signalling and activation of TRPV1 by anandamide, and that seemed to involve increased AMPAR internalization. However, in this study, LTD could only be abolished by blocking both TRPV1 and CB1 receptors, suggesting that anandamide acts as an endocannabinoid and an endovanilloid to cause LTD.

The authors found that TRPV1- and CB1-dependent LTD was absent in NAc slices from mice following *in vivo* cocaine exposure, and that *Trpv1*$^{-/-}$ mice displayed increased behavioural sensitization to the drug, indicating that drug-induced impairments in these mechanisms of LTD might underlie behavioural correlates of addiction.

These papers suggest that activation of postsynaptic brain TRPV1 receptors by anandamide might represent an important mechanism of LTD in specific pathways and could be implicated in neuroadaptations underlying drug dependence.

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ORIGINAL RESEARCH PAPERS Chavez, A. E. *et al.* TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. *Nature Neurosci.* **13**, 1511–1518 (2010) | Grueter, B. A. *et al.* Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. *Nature Neurosci.* **13**, 1519–1525 (2010)