potentiation (cLTP), which results in spine enlargement, by treating cultured cortical neurons with glycine. Live confocal imaging of the neurons for 3 hours after treatment, followed by retrospective labelling for PSD95 and VGLUT1, revealed that dendritic spines that had increased in size in this period exhibited more PSD95- and VGLUT1-containing clusters than those that did not respond to glycine treatment.

These findings suggested that both presynaptic and postsynaptic protein clusters scale up in a coordinated manner during cLTP-induced spine enlargement. Indeed, live-cell STED imaging of neurons expressing fluorescently-labelled PSD95 or SYP showed that the number of presynaptic or postsynaptic protein clusters increases rapidly in individual dendritic spine synapses undergoing structural plasticity and is significantly higher in these synapses than in those that do not respond to cLTP 2 hours after its induction. Further analysis showed that this increase in the number of nanomodules at the synapse was preceded by a rise in their mobility; however, the clusters of presynaptic and postsynaptic proteins remained in close alignment at all times, adding further support to the idea that they form a functional trans-synaptic unit.

These findings suggest that excitatory synapses are made up of individual nanomodules consisting of aligned clusters of presynaptic and postsynaptic proteins and highlights the importance of coordinated changes in both presynaptic and postsynaptic proteins for cLTP. Structural plasticity appears to be mediated, at least in part, by changes in the number of nanomodules present at each synapse and the mechanisms by which new nanomodules are added to a dendritic spine, as well as those by which their precise pre–post synaptic alignment is maintained, will be an important focus for future studies.

Katherine Whalley

ORIGINAL ARTICLE Hruska, M. et al. Synaptic nanomodules underlie the organization and plasticity of spine synapses. *Nat. Neurosci.* https://doi.org/10.1038/s41593-018-0138-9 (2018)

Credit: Hero Images/Getty

Indeed, optogenetic inhibition of ACC→BLA neurons as mice observed demonstrator mice interacting with an aggressive strain mouse rendered the observer mice less likely to avoid the aggressive mouse in a subsequent three-chamber test. Furthermore, the same light-induced inhibition of ACC→BLA neurons as observer mice watched demonstrator mice interact with a juvenile intruder mouse led the observer mice to subsequently spend less time interacting with the juvenile mouse.

Together, these results provide evidence that the ACC transmits socially derived information (in this case, the distress of the shocked demonstrator mice) to the BLA, which in turn encodes the aversive value of the cue for observational learning.

Natasha Bray

ORIGINAL ARTICLE Allsop, S. A. et al. Corticoamygdala transfer of socially derived information gates observational learning. *Cell* https://doi.org/10.1016/j.cell.2018.04.004 (2018)

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NEUROPHARMACOLOGY

A pathway less travelled

Opiate drugs such as morphine exert their pharmacological effects by binding to opioid receptors (ORs), the endogenous ligands for which are opioid peptides. Whether opiate drugs have additional OR-mediated effects that are not produced by their peptide counterparts is not clear. Stoeber et al. now show that OR activation in neurons occurs at both cell-surface and intracellular sites, and that opioids and opiates activate ORs at different intracellular compartments.

Here, the authors developed 'conformational biosensors' that bind specifically to the activated conformation of μ-ORs and δ-ORs (MORs and DORs, respectively). These sensors were fused with a fluorescent protein tag to report when and where ligands activated OR, and enabled precise temporal and spatial monitoring of OR conformational changes at both surface and intracellular locations in real time in living cells.

Binding of opioid peptides to MOR and DOR in the plasma membrane (PM) promotes rapid internalization and targeting to endosomes. On application of a peptide agonist to cultured non-neural cells expressing ORs and the OR sensor, fluorescence accumulated steadily at endosomes over 20 minutes. The signal persisted after washout of the OR agonist, but was reversed by application of a membrane-permeant antagonist. Moreover, DOR-mediated inhibition of cyclic AMP (cAMP) accumulation continued after washout of the peptide agonist, suggesting that internalized ORs are activated and continue to participate in cell signalling.

The authors then expressed fluorescently tagged ORs and the OR sensor in primary cultures of striatal medium spiny neurons, which express ORs at the PM, in endosomes, at somatic Golgi apparatus and at dendritic Golgi outposts. Application of a selective MOR peptide agonist led to a relocation of colocalized MORs and OR sensors from the PM to endosomes, suggesting that active-conformation MORs at endosomes have bound ligands. This was rapidly reversed by membrane-permeant MOR antagonist naloxone. Similar results were obtained for DOR-selective activation and for activation by endogenous opioids β-endorphin and met-enkephalin.

By contrast, application of membrane-permeant, non-peptide agonist morphine resulted in OR-sensor recruitment within seconds at somatic Golgi apparatus and dendritic Golgi outposts — much faster than peptide agonist-induced internalization. Crucially, morphine did not appear to activate endosomal ORs and peptide agonists failed to recruit the OR sensor to Golgi. Again, OR-sensor fluorescence could be reversed by application of a membrane-permeant antagonist.

Overall, these findings show that opioid peptides and opiate drugs produce different spatiotemporal patterns of OR activation in striatal neurons.

Sian Lewis

ORIGINAL ARTICLE Stoeber, M. et al. A genetically encoded biosensor reveals location bias of opioid drug action. *Neuron* https://doi.org/10.1016/j.neuron.2018.04.021 (2018)