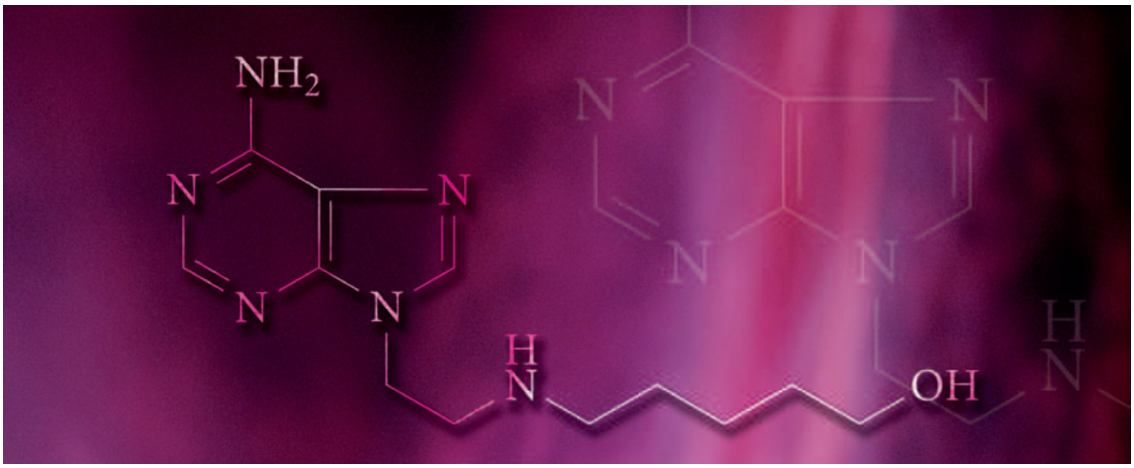
ANALGESIA

Inhibiting neuropathic pain



> an orally available inhibitor of adenylyl cyclase 1 (AC1) inhibits neuropathic pain in animal models

There are limited treatment options available for alleviating neuropathic pain, which is often caused by nerve injury. Now, a study published in *Science Translational Medicine* has identified an orally available inhibitor of adenylyl cyclase 1 (AC1) that inhibits neuropathic pain in animal models.

AC1 is involved in pain-related synaptic changes (that is, long term potentiation; (LTP)) in the spinal cord dorsal horn and the anterior cingulate cortex, and is primarily expressed in neurons, making it a neuron-specific target for analgesia. To identify inhibitors of AC1, the authors screened compounds that had structural similarity to the non-selective AC activator forskolin and the AC substrate ATP for their ability to inhibit AC1 in a cellular assay. This identified a compound — named NB001 — that showed ≥tenfold selectivity for AC1 over other AC isoforms and was selected for further study. NB001 inhibited glutamate-stimulated cyclic AMP production in mouse brain slices and in human neuroblastoma cells, with IC_{50} values in the low micromolar range.

Next, the authors investigated the analgesic effects of NB001. When it was administered intraperitoneally (0.1 mg per kg) or orally (1 mg per kg), NB001 reduced behavioural allodynia — pain perceived in response to a usually innocuous stimulus — in a mouse model of neuropathic pain. The analgesic effect of the orally administered compound lasted for at least 2 hours. Administration of 1–3 mg per kg of NB001 (via intraperitoneal injection) also showed analgesic effects in a mouse model of inflammatory pain, although this dose was less efficacious in inflammatory pain than in neuropathic pain.

Further studies to determine the site of action of NB001 (for example, the brain, the spine or the periphery) indicated that this compound probably acts centrally at supraspinal sites to produce its analgesic effects. In addition to acting on the anterior cingulate cortex, the compound possibly acts at other cortical and subcortical sites. NB001 did not affect acute nociception, anxiety-like behaviour or motor function of mice at analgesic doses. Importantly, it did not affect hippocampal LTP, which is important for the formation of new memories.

NB001, which targets pain-related synaptic plasticity, could therefore be a lead for the identification of compounds with greater efficacy and selectivity for AC1, which could potentially be used for the treatment of neuropathic pain.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Wang, H. *et al.* Identification of an adenylyl cyclase inhibitor for treating neuropathic and inflammatory pain. *Sci. Transl. Med.* **3**, 65ra3 (2011)