ACS Chemical Neuroscience

In This Issue

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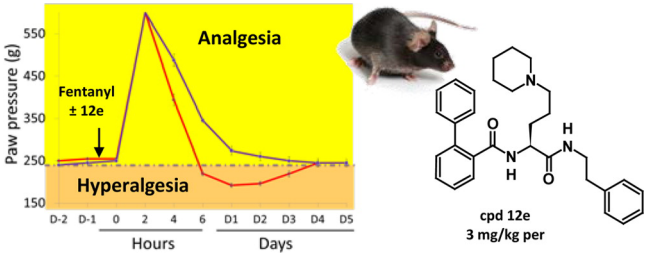
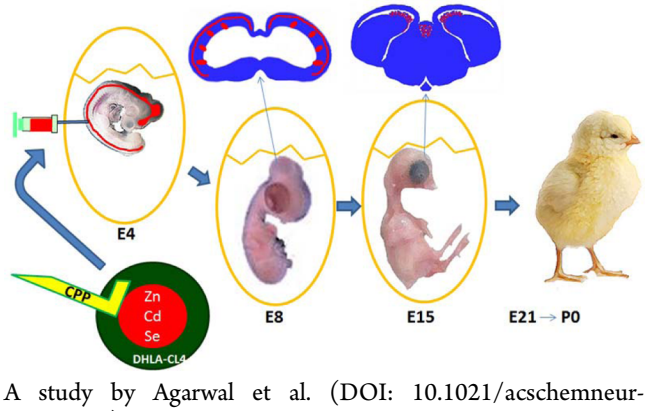
REDUCING SIDE EFFECTS OF PAIN MEDICATION



Opiate analgesics, such as morphine, continue to be the cornerstone medication for treating moderate to severe pain, but their use suffers from important side effects such as tolerance, addiction, and hyperalgesia. A part of these side effects was associated with antiopioid systems, including neuropeptide FF receptors (NPFFR). A few years ago, researchers developed the first NPFF-receptor antagonist (RF9), and its coadministration with opioids led to a block of both associated hyperalgesia and tolerance. However, the dipeptidic nature of RF9 limited its application to intravenous administration. In the current issue, Bihel et al. (DOI: 10.1021/cn500219h) work to establish a structure−activity relationship study of RF9 in order to develop a peptidomimetic NPFFR antagonist.

The authors managed to design innovative non-natural ornithine derivatives. Among them, compound **12e** was able to prevent the opioid-induced hyperalgesia at low dose after oral administration, and it shows a safe profile in terms of selectivity (off-targets) or clinical observation (general comportment, motricity, food intake, etc.). This work constitutes an interesting proof-of-concept of the emergence of new therapeutic tools in the field of pain treatment.

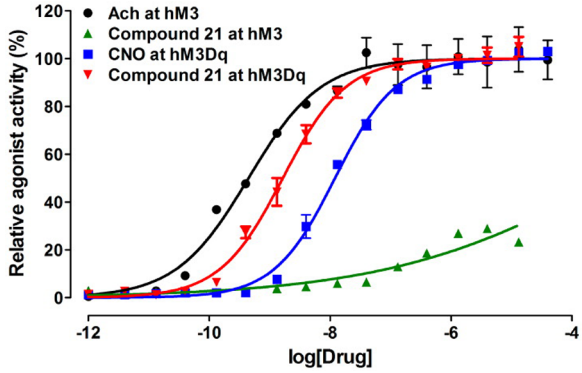
DELIVERING THERAPEUTIC CHEMICALS TO THE BRAIN



A study by Agarwal et al. (DOI: 10.1021/acschemneuro.5b00022), in the current issue, shows that carefully designed and chemically synthesized fluorescent nanoparticles (quantum dots, QDs) can be delivered to all parts of the developing brain following microinjection into the spinal canal. The authors had previously shown in cultured cells and brain slices that by coating the QDs with a negatively charged polymer, it is possible to target neurons. Additionally, by incorporating 6 histidine residues into the drug (WGDap(Palmitoyl)VKIKK-P9GGH6), it is possible to tightly bind it to the Zn on the surface of the QD and promote both uptake by and egress from endosomes.

The authors now use a number of techniques to clearly show that these QDs are well-distributed and not toxic to the living developing chick brain. The study opens up the field of delivering therapeutic chemicals to the brain, with the added advantage that we can track the fate of the particles in a living brain.

NEXT GENERATION DREADD LIGANDS



Over the past decade, two independent technologies have emerged and been widely adopted by the neuroscience community for remotely controlling neuronal activity: optogenetics which utilize engineered channelrhodopsin and other opsins, and chemogenetics which utilize engineered G protein-coupled receptors (Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)). Using directed molecular evolution, two types of DREADDs derived from human muscarinic acetylcholine receptors have been developed: hM3Dq which activates neuronal firing, and hM4Di which inhibits neuronal firing. Importantly, these DREADDs were not activated by the native ligand acetylcholine, but selectively activated by clozapine *N*-oxide (CNO), a pharmacologically inert ligand. CNO has been used extensively in rodent models to activate DREADDs, and although CNO is not subject to significant metabolic transformation in mice, a small fraction of CNO is apparently metabolized to clozapine in humans and guinea pigs, lessening the translational potential of DREADDs.

In the current issue, Chen et al. (DOI: 10.1021/cn500325v) report the first structure−activity relationship studies of hM3Dq. The authors explored multiple regions of the scaffold represented by CNO, and discovered several compounds that are very potent hM3Dq agonists but do not activate the native human M3 receptor (hM3). The authors also discovered that the approved drug perlapine is a novel hM3Dq agonist with >10 000-fold selectivity for hM3Dq over hM3.

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