ACS Chemical Neuroscience

IN THIS ISSUE

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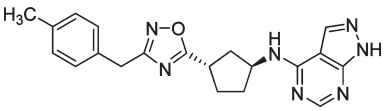
Diminishing Neuropathic Pain and Parkinson's Disease



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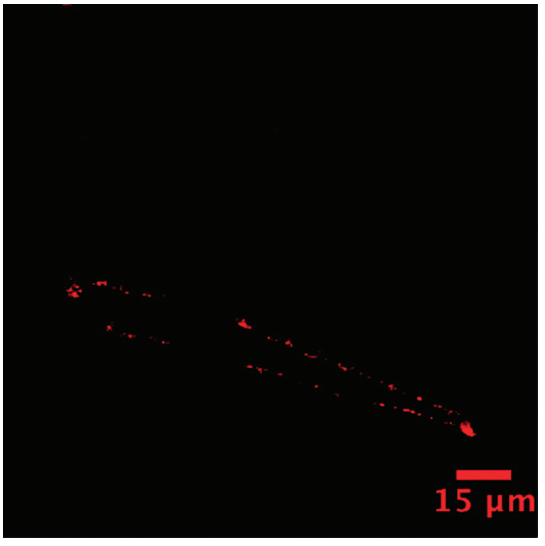
Ubiquitous in the central nervous system, the *N*-methyl-D-aspartate (NMDA) receptor mediates synaptic transmission upon stimulation by glutamate and glycine. Abnormal triggering of these receptors has been implicated in several neurological conditions, particularly in neuropathic pain and Parkinson's disease. The identification of compounds that lower the activity of these receptors is therefore of clinical importance. Layton et al. (DOI: 10.1021/cn200013d) report the development of an effective new compound that antagonizes the NMDA receptor subunit, NR2B.

NMDA receptors are heteromultimeric protein complexes composed of several functional subunits. Previous studies have shown that antagonizing the NR2B subunit of NMDA receptors results in a reduction in neuropathic pain and Parkinson's disease in animal models. The authors used their previously identified phenol-containing NR2B antagonist, and rationally designed and optimized a new series of compounds that can be administered orally to efficiently reduce neuropathic pain and Parkinson's disease in preclinical models.

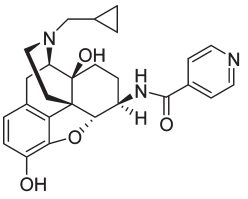
Visualization of Dopamine Transporters in Real Time



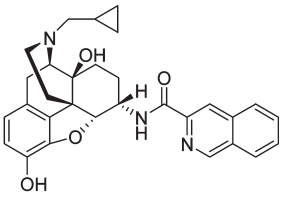
Dopamine (DA) is a well-known neurotransmitter that plays a role in behavioral responses. Aberrant DA modulation is linked to several psychiatric and neurodegenerative disorders. The presynaptic DA transporter (DAT) is important to normal DA signaling and is a major target for recreational drugs such as cocaine and amphetamines. To date, several questions remain regarding the functioning and location of this clinically important transporter due to lack of suitable fluorescence probes. Kovtun et al. (DOI: 10.1021/cn200032r) report the development of a simple and rapid approach for visualizing DAT with high spatiotemporal resolution.

A potent DAT-specific cocaine analogue, biotinylated 2-β-carbomethoxy-3- β-(-4-fluorophenyl)-tropane, conjugated with streptavidin-bound quantum dot semiconductor nanocrystals, was used to visualize DAT in live mammalian cells at superior resolution. This approach was also successfully applied to study protein-kinase-C-dependent DAT-trafficking. This new methodology is a useful tool allowing researchers to visualize molecules at high spatial and temporal resolution, furthering our understanding of DAT location and function and contributing to the ultimate goal of clinically addressing neurodegenerative and psychiatric illnesses.

Novel Antagonists to Opioid Receptors



NAP



NAQ

Opioid receptors have been linked to several diseases of the central and peripheral nervous systems. One such receptor, the Mu opioid receptor (MOR) is a target for palliative opiates, but is also implicated in side effects associated with these drugs. The development of specific antagonistic compounds to MOR is desirable for structural and functional characterization. Currently, only peptide-based antagonists for this receptor exist which suffer from poor pharmacokinetic characteristics and bioavailability. In this issue, Yuan et al. (DOI: 10.1021/cn2000348) report the development of two novel nonpeptidyl lead compounds of high therapeutic significance.

Using rigorous pharmacological studies on a series of 6α- and 6β-*N*-heterocyclic substituted naltrexamine derivatives, the authors identified compounds NAP and NAQ as highly specific reversible antagonists of MOR. Upon further characterization, NAP was determined to target the peripheral nervous system, whereas NAQ exerted its effects on the central nervous system. The identification of these two novel lead compounds offers fresh insight to stimulate future studies of opioid receptors in both the peripheral and central nervous system.

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