ACS Chemical Neuroscience

In This Issue

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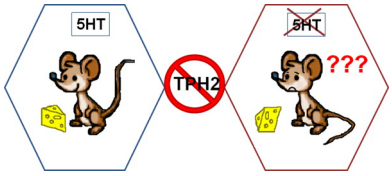
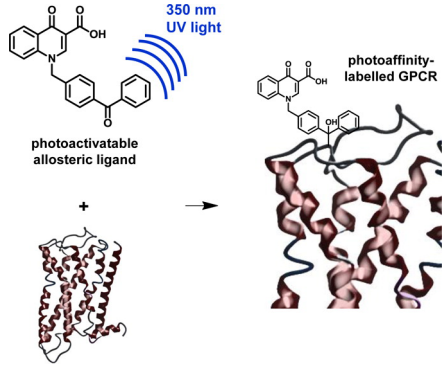
RETHINKING THE CHEMICAL BASIS FOR DEPRESSION



For over 50 years, defects in serotonin function have been thought to be the underlying cause of depression. Today, the most widely used therapy for treating this debilitating disorder is the use of selective-serotonin-reuptake inhibitors. However, the best known treatments leave ∼60−70% of patients without symptomatic relief. In this issue, a study by Angoa-Pérez et al. (DOI: 10.1021/cn500096g) questions the role of serotonin in depression.

The authors developed a mouse lacking the gene for the brain-specific form of tryptophan hydroxylase, TPH2, which is an essential enzyme involved in the biosynthesis of serotonin. Surprisingly, the authors found that these TPH2$^{-/-}$ mice showed no signs of depression-like behavior when compared to wild-type controls. This result throws into question the role of serotonin as an etiological factor in depression and serves as an important starting point for developing new treatments.

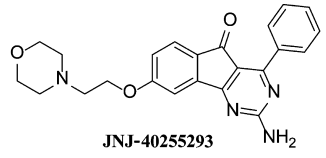
PHARMACOLOGICAL TOOL FOR STUDYING mACh RECEPTOR



Activation of the M_1 muscarinic acetylcholine receptor (mAChR) is a promising treatment approach for alleviating the cognitive decline experienced in central nervous system disorders such as Alzheimer's disease and schizophrenia. Current therapeutics indiscriminately enhance the activity of the endogenous neurotransmitter acetylcholine that, through activation of other mAChR subtypes, leads to debilitating side effects. In current issue, Davie et al. (DOI: 10.1021/cn500173x) report the development of a specific photoactivatable ligand for mAChR, a new tool for deciphering the precise role of these receptors in neurological disorders.

The authors added a benzophenone group for photoactivatable functionality to the selective M_1 mAChR positive allosteric modulator, benzyl quinolone carboxylic acid (BQCA), to produce a compound of high subtype selectivity and a more fine-tuned mode of action typical of allosteric ligands. The authors provide validation of this photoactivatable allosteric modulator (called "MIPS1455") and demonstrate irreversible binding to the M_1 mAChR. This work successfully identifies a ligand that has the potential to serve as an important pharmacological tool with a range of applications.

NEW COMPOUND AIMED AT PARKINSON'S DISEASE



Human adenosine receptor functional activity (EC_{50}, nM)

	A_1	A_{2A}	A_{2B}	A_3
JNJ-40255293	48 ± 16	6.5 ± 3.8	230 ± 92	9200

Adenosine A_{2A} receptor antagonists continue to be a potential target to treat Parkinson's disease. There have been several reports that highlight new medicinal chemistry approaches aimed at this attractive and promising target. The target is clinically validated, and there have been a number of compounds that have entered clinical trials for the indication. In the current issue, Atack et al. (DOI: 10.1021/cn5001606) provide detailed in vivo characterization of JNJ-40255293, a dual adenosine A_{2A} antagonist.

This authors highlight the dual A_{2A}/A_1 antagonist, JNJ-40255293, in a variety of animal models for Parkinson's disease. Also discussed are the results of JNJ-40255293 in behavioral studies that assess the effects of the compound on sleep/wake cycles, REM sleep, drug dependency, and conditioned avoidance. Overall, the compound showed promise in experimental models of Parkinson's disease, and validates the adenosine A_{2A} receptor as a target for treating this neurodegenerative disorder.

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