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In This Issue

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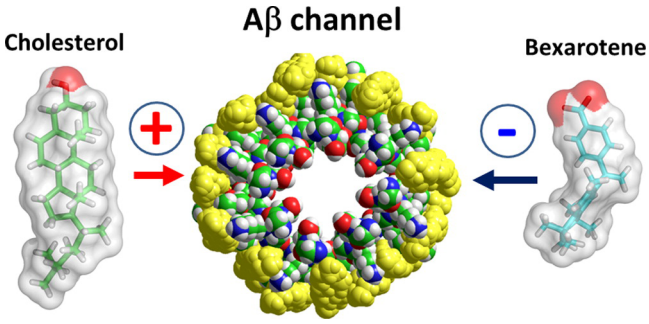
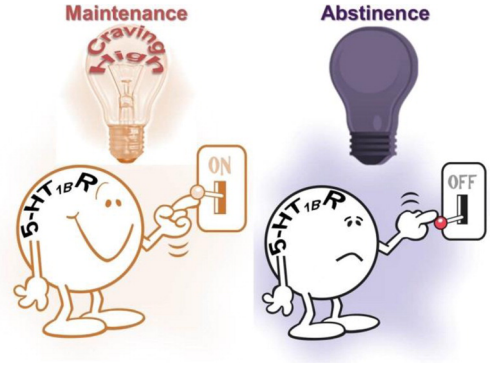
BEXAROTENE—NEW ANTI-ALZHEIMER'S PROTOTYPE COMPOUND



The root cause of Alzheimer's disease has many hypotheses. A commonly held view is that pathology is caused by the deposition of large aggregates of proteins in the brain (amyloid plaques). Another view, however, is that the assembly of small annular structures (amyloid channels) makes holes in brain cells and perturbs calcium fluxes. In the current issue, Fantini et al. (DOI: 10.1021/cn400183w) demonstrate that cholesterol stimulates the assembly of these neurotoxic amyloid channels.

The authors show that a compound (bexarotene), which impairs the binding of cholesterol to amyloid proteins, efficiently blocks the formation of these channels. Bexarotene has previously been shown to improve memory in mice with Alzheimer's disease, but its mechanism of action was uncertain. This study opens a promising therapeutic approach for Alzheimer's disease.

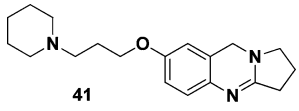
A NOVEL TARGET FOR TREATING COCAINE ADDICTION



Serotonin-1B (5-HT_{1B}) receptors have previously been linked to substance abuse. However, the modulatory effects of these receptors with regard to cocaine self-administration and cocaine-seeking behavior have been unclear. Now, Pentkowski et al. (DOI: 10.1021/cn400155t) elucidate the role of 5-HT_{1B} receptors in mediating cocaine-abuse-related behaviors in rats.

The authors examined effects of the selective 5-HT_{1B} receptor agonist CP 94,253 on cocaine intake and cocaine-seeking behavior at different time points during abstinence. They found that CP 94,253 reduced cocaine intake in both schedules of reinforcement, regardless of the cocaine dose or extinction history, and attenuated cue- and cocaine-primed cocaine-seeking behavior after 5 days, but not after 1 day of abstinence. The authors suggested that the effect of 5-HT_{1B} receptor stimulation on cocaine-abuse-related behaviors depended on the duration of abstinence from psychostimulant self-administration. These preclinical findings indicate that 5-HT_{1B} receptors may serve as suitable pharmacological targets for treating cocaine dependence.

TARGETING ALZHEIMER'S VIA DUAL INHIBITORS



K_i (hH_3) = 76.2 nM
IC_{50}(*h*AChE) = 33.9 nM
IC_{50}(*Ee*AChE) = 66.5 nM

Dual-acting AChE inhibitor / hH_3 antagonist

Acetylcholinesterase (AChE) is a "classical" cognition improving target of Alzheimer drugs. Additionally, histamine H3 receptor has been implicated in several cognitive disorders, including Alzheimer's disease. In the current issue, Darras et al. (DOI: 10.1021/cn4002126) provide potent dual inhibitors that take aim at these two targets of interest for the treatment of Alzheimer's disease.

The authors developed dual inhibitors comprising tri- and tetracyclic nitrogen-bridgehead compounds of structural families previously reported as cholinesterase inhibitors with the 3-(1-piperidinyl)propoxy moiety that is present in several known classes of H3 antagonists. Two different SARs performed on the compounds were accompanied by computational studies at both targets, based on an advanced docking technique at AChE and molecular dynamics simulations at the H3 receptor. These combined efforts led to the identification of compounds that are able to act at both targets in the desired way in the same low concentration range.

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