ACS Chemical Neuroscience

In This Issue

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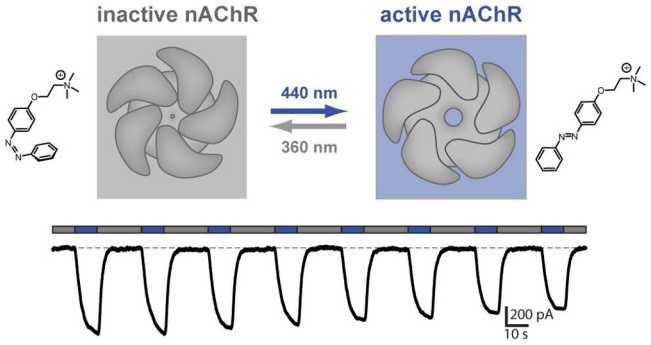
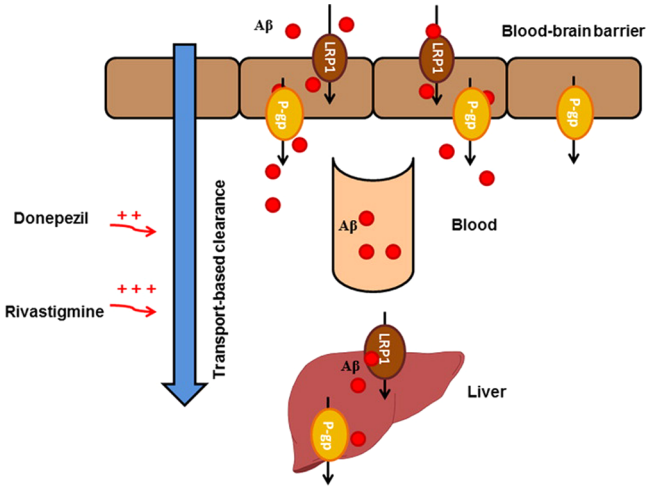
AZOCHOLINE FACILITATES NICOTINIC ACETYLCHOLINE RECEPTOR MODULATION



Nicotinic acetylcholine receptors (nAChRs) are essential for cellular communication in higher organisms. In the current issue, Damijonaitis et al. (DOI: 10.1021/acschemneuro.5b00030) report the development, synthesis, and application of photochromic agonists for nAChRs. In particular, the authors introduce AzoCholine, which enables the optical control of the neuronal α7 nAChRs in vitro and ex vivo. It can be used to perturb the swimming behavior of the nematode *Caenorhabditis elegans*, demonstrating its applicability.

The authors demonstrate that AzoCholine activates neuronal α7 nAChR heterologously expressed in HEK cells and native to dissociated rat dorsal root ganglion cells. In addition, network activity could be modulated, as demonstrated by multielectrode array recordings from acute mouse hippocampal brain slices. Furthermore, the swimming behavior of *C. elegans* could be controlled with AzoCholine and irradiation. AzoCholine effectively turns α7 nAChRs into photoreceptors and does not require genetic manipulation. By varying the irradiation wavelengths, the concentration of the active form of AzoCholine can be adjusted in a graded fashion ("photodosing"). Thus, it is now feasible to control endogenous nAChRs with high spatiotemporal precision. This will be instrumental for elucidating their roles in the nervous system and may prove to be therapeutically useful as well.

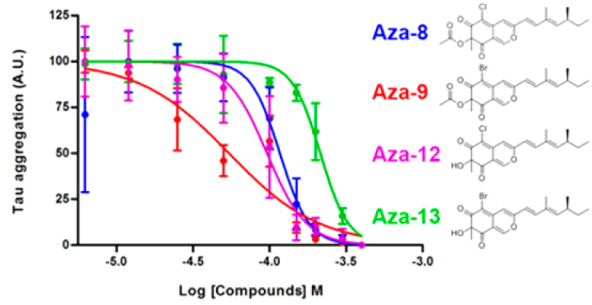
NEUROPROTECTIVE EFFECT OF CHOLINESTERASE INHIBITORS



Donepezil and rivastigmine are used to ease the symptoms of dementia associated with Alzheimer's disease However, recent investigations have reported both drugs to provide neuroprotective and disease-modifying effects. In the current issue, Mohamed et al. (DOI: 10.1021/acschemneuro.5b00040) investigated a new mechanism by which these two cholinesterase inhibitors (ChEIs) provide neuroprotective effect against Alzheimer's disease.

The authors used in vitro cell culture and in vivo animal studies to investigate the effect of 1 month treatment on amyloid-β, a hallmark of Alzheimer's disease, level in the brain. Their results showed both drugs were able to increase brain and hepatic clearance of amyloid-β. This enhancement was explained, at least in part, to the drugs' ability to upregulate amyloid-β transport proteins, LRP1 and P-gp, localized at the blood-brain barrier and hepatocytes. These results are significant as they provide an additional mechanism by which these drugs provide neuroprotective effect, in addition to their established effect to ease the symptoms of dementia associated with Alzheimer's disease by enhancing acetylcholine levels in the brain. These results also support optimizing donepezil and rivastigmine clinical use for the prevention and/or treatment of Alzheimer's disease.

NEW TAU AGGREGATION INHIBITORS



Natural products from fungi have provided many medically useful compounds, such as penicillin, but they have been difficult to purify, identify, and synthesize. Using advanced molecular genetic approaches, it is now possible to engineer fungi to overproduce large amounts of unique compounds to test their medicinal properties. Using this approach, Paranjape et al. (DOI: 10.1021/acschemneuro.5b00013) report that certain azaphilone compounds are capable of preventing and reversing the aggregation of an Alzheimer's disease related protein.

The authors previously reported that the secondary metabolite from *Aspergillus nidulans*, asperbenzaldehyde, inhibited the aggregation of tau protein into fibrils. Because asperbenzaldehyde is a precursor to azaphilone biosynthesis, the authors presented the next step in which they examine the tau aggregation inhibition properties of azaphilones. Paranjape et al. found that most azaphilones also inhibit tau aggregation, but more significantly, a subset of the compounds dissolve preformed filaments. Based on the structure–activity relationships

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of the compounds, they identified the sites on the compound scaffold that seem most promising for further development of enhanced tau aggregation inhibitors. This is an exciting result because it provides a new chemical structure that could be manipulated to make new drugs for Alzheimer's disease, which currently lacks treatments that reduce the amounts of pathology.

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