ACS Chemical Neuroscience

In This Issue

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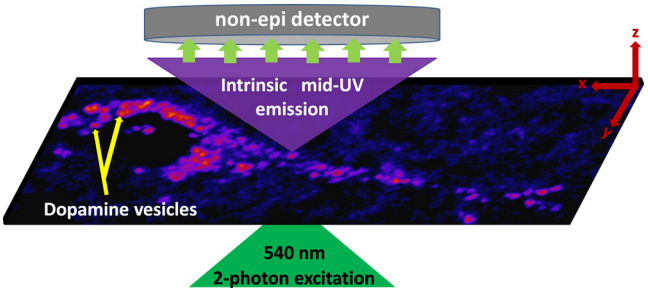
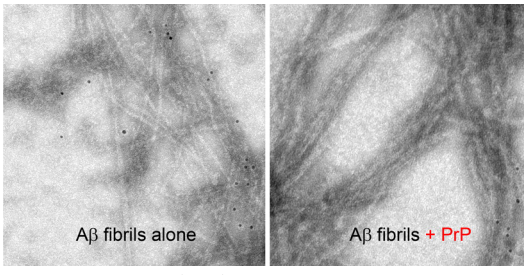
IMAGING DOPAMINE IN LIVING NEURONS



Dopamine is a neurotransmitter which mediates a myriad of human experiences. It functions as a reward molecule in the brain that results in euphoria and helps with learning. Dopamine is also involved in motor control. The dysfunction of this pathway is the underlying cause of Parkinson's disease. Drugs of abuse, such as cocaine and amphetamine, mediate their effects by releasing copious quantities of dopamine from the dopaminergic neurons. Therefore, a microscope that can directly visualize dopamine in individual cells would benefit a large number of related fields, with significant clinical implications. In the current issue, Sarkar et al. (DOI: 10.1021/cn5000138) image dopamine in a label-free manner, at sub-micrometer resolution inside live neurons in a brain slice.

The authors present the first demonstration of imaging endogenous dopamine in living neurons. To achieve this feat, they developed a new methodology which takes advantage of the intrinsic midultraviolet autofluorescence of dopamine. By combining two-photon excitation with a non-epifluorescence detection system, the authors were able to image dopamine with sub-micrometer resolution while avoiding the usual problems of UV phototoxicity and transmission.

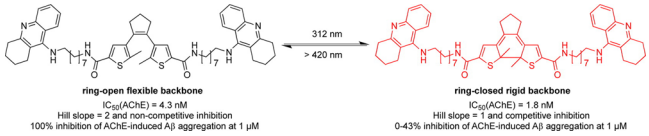
ELUCIDATING THE PRION PROTEIN–Aβ INTERACTION MECHANISM



Alzheimer's disease (AD) is the most common neurodegenerative disorder. It is believed that one of the main culprits in the disease is toxic assemblies formed by a 40–42 amino acid residue peptide known as Aβ peptide. Recent data point to a potentially critical disease pathogenesis role of the interaction between some of these Aβ assemblies and the prion protein (PrP). In the current issue, Nieznanski et al. (DOI: 10.1021/cn500019c) study the mode of Prp–Aβ interaction and reveal some findings which have important implications for current efforts to develop PrP-based compounds as potential drugs against AD.

The authors show that, in addition to previously demonstrated binding of PrP to small soluble Aβ oligomers, prion protein also interacts with larger, highly ordered aggregates of Aβ known as amyloid fibrils. However, in contrast to previous suggestions that PrP causes disassembly of Aβ fibrils into more toxic oligomers, no such disassembly could be detected in the present study. Here, atomic force microscopy and electron microscopy consistently indicate that the main consequence of PrP interaction with Aβ fibrils is bundling of individual fibrils into larger aggregates.

INVESTIGATING THE ROLE OF ACETYLCHOLINESTERASE IN ALZHEIMER'S DISEASE



Over the past few years, cholinesterase inhibitors have emerged as potential therapeutics because acetylcholinesterase (AChE) might play a role in the formation of Aβ deposits. In the current issue, Chen et al. (DOI: 10.1021/cn500016p) identified and fully characterized a novel biological tool to investigate the different roles of AChE in healthy and disease states, which may serve as an inspiration for researchers to apply photoswitchable molecules in neuroscience research.

The authors describe the development of tacrine-based inhibitors of AChE, a core enzyme for the treatment of Alzheimer's disease, with several biological functions. These inhibitors are photoswitchable; that is, two stable photoisomers exist that can be converted into each other by use of visible or UV light. Additionally, the compounds are nanomolar inhibitors in both photoforms, but one compound changes its binding mode from univalent to bivalent after irradiation. The authors used computational docking studies as well as MD simulations to investigate whether the second interaction site of the bivalently acting photoform is the so-called PAS ("peripheral anionic site"), the inhibition of which reduces the ability of AChE to catalyze β-amyloid aggregation. Kinetic studies and a β-amyloid aggregation assay proved that a potent enzyme inhibitor had been identified which can be "switched on" by light to selectively also block the PAS and therefore β-amyloid aggregation.

Published: May 21, 2014

dx.doi.org/10.1021/cn5000887 | *ACS Chem. Neurosci.* 2014, 5, 325–325