ACS Chemical Neuroscience

In This Issue

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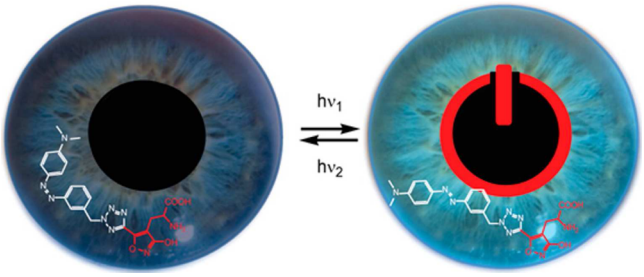
NOVEL CLASS OF COMPOUND FOR VISION RESTORATION



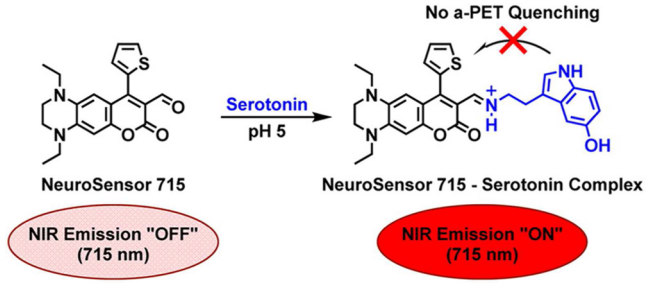
In recent years, photopharmacology has emerged as a powerful technique to optically control biological activity, including the restoration of vision without the need of genetic manipulations. In the current issue, Laprell et al. (DOI: 10.1021/acschemneuro.5b00234) introduce a recently published AMPA receptor specific photochromic ligand (PCL), ATA, for the restoration of vision. This molecule is active in its dark-adapted *trans*-isoform, becomes inefficacious when irradiated with blue or white light, and switches back to its *trans*-isoform within milliseconds after turning off the light. This allows to reversibly control AMPA receptor activity with light, as has been previously shown in cortical neurons.

In the current issue, the authors validate that ATA in the retina selectively activates AMPA receptors. Multielectrode array recordings in combination with different pharmacological approaches demonstrate that the overall light response in retinal ganglion cells is primarily shaped by amacrine cell and retinal ganglion cell activation. A short preincubation of 3 min with low ATA concentration (25 μM) is sufficient to photosensitize the retina for several hours ex vivo.

ATA bears several new features. First, it exhibits a higher solubility in aqueous solution than previous photopharmaceuticals investigated for the restoration of vision. Therefore, no additional excipients are needed. Second, it operates on ligand-gated ion channels as opposed to voltage-gated ion channels. And third, it functions as a photoswitchable agonist and not as a photochromic blocker. As such, ATA-mediated stimulation provides a more natural stimulus mimicking excitatory synaptic transmission.

With this work, the authors prove that freely diffusible photochromic receptor agonists are able to confer light sensitivity to blind retinae, without the need of constant application. Therefore, ATA establishes a novel class of PCLs for vision restoration approaches and it paves the way for the development of next-generation photochromic receptor agonists.

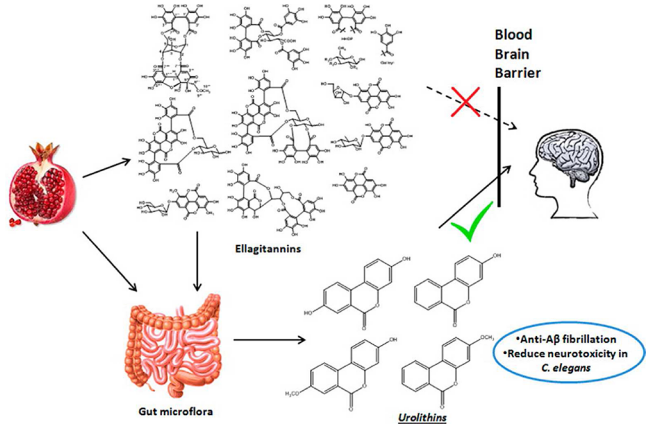
IMAGING SEROTONIN



Over the years, serotonin has been an important and particularly troublesome analyte to detect in cells because it is the most quenching of all the primary amine neurotransmitters. In the current issue, Hettie and Glass (DOI: 10.1021/acschemneuro.5b00235) describe a novel method for designing a working serotonin sensor based on computational studies. The authors show that the sensor works as expected spectroscopically and validate the findings in proven cell assay.

More specifically, a near-infrared fluorescent probe for a serotonin is studied in this work. On the basis of a DFT calculation, the authors designed and synthesized a courmarin-3-aldehyde-based compound called NeuroSensor 715 (NS715) as a potential fluorescent sensor for serotonin. The authors found that, in aqueous solution at pH = 5, this compound exhibits fluorescent enhancement in the near IR region. It shows much better affinity with serotonin than with other monoamines. The authors further studied the use of NS715 to image cells with either the norepinephrine-enriched or epinephrine-enriched chromaffin cells and found greater fluorescent enhancement in the NS715 treated norepinephrine-enriched cells. The fluorescent probe described in this paper is novel and robust for imaging this neurotransmitter.

AN ANTI-ALZHEIMER'S COMPOUND FROM POMEGRANATE



The health benefits of consuming pomegranates have been attributed to its major chemical constituent, ellagitannins. Pomegranate natural products have been shown to prevent

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Alzheimer's disease (AD) pathogenesis in several transgenic AD animal models. The anti-AD effects of an ellagitannin-rich pomegranate extract (PE) in an aged transgenic animal model were recently reported. However, to date, the bioactive compounds, whether the naturally occurring pomegranate ellagitannins and/or their physiologically relevant gut microflora derived metabolites (known as urolithins), are not known.

In the current issue, Yuan et al. (DOI: 10.1021/acschemneuro.5b00260) identified 21 constituents, predominantly ellagitannins, from the PE and elucidated their structures by NMR and mass spectroscopy methods. Using in silico computational methods, the authors showed that none of the PE isolates, but the urolithins, fulfill criteria required for blood-brain barrier penetration. The urolithins prevented β-amyloid fibrillation in vitro and had a protective effect in *Caenorhabditis elegans* post induction of amyloid β1−42 induced neurotoxicity and paralysis. Therefore, urolithins are the likely brain absorbable metabolites contributing to PE's anti-AD effects, warranting further in vivo studies with these purified compounds.

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