ACS Chemical Neuroscience

In This Issue

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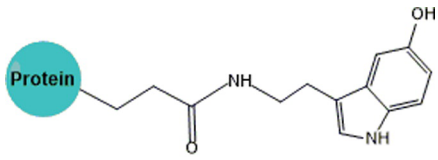
SEROTONYLATION – A UNIQUE POSTTRANSLATIONAL MODIFICATION

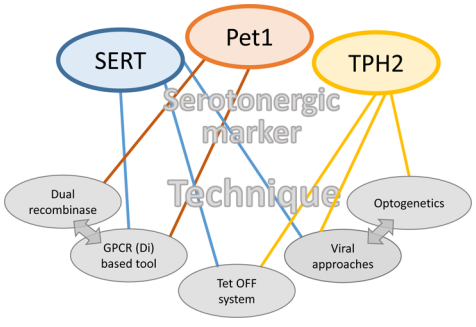


Serotonylated Protein

There is growing evidence for transglutaminase (TGase)-mediated serotonylation and more generally, monoaminylation in the central nervous system. In the current issue, Hummerich et al. (DOI: 10.1021/cn5003286) sought to identify further neural target proteins for this posttranslational protein modification. To this aim, they performed TGase-mediated transamidation of the fluorescent monoamine monodansylcadaverine (MDC) to glial proteins followed by UV visualization of MDC-labeled proteins and identification by mass spectrometry. Mass spectrometric analysis of MDC-labeled peptides clearly identified all three subunits of fibrinogen, as well as several glia-derived proteins as substrates for TGase-mediated monoaminylation, including the respective modified glutamine residues.

Muma and Mi (DOI: 10.1021/cn500329r) provide a broad and informative summary of serotonylation research since its discovery at the beginning of this millennium. After an introduction on general aspects of serotonylation and monoaminylation and the respective enzymes (TGases), the authors provide key details on different methods for detecting monoaminylation, targets for monoaminylation, and their possible roles in exocytotic events in different cell types. Moreover, the possible impact of different monoamine transporters on monoaminylation is discussed and the expression and function of the different TGases are summarized.

DESIGNER TOOLS FOR ANALYZING SEROTONERGIC CIRCUITS



Serotonin, acting as a neurotransmitter in the brain, participates in neural circuits controlling a wide variety of physiological and behavioral functions. Serotonergic neurons are located in the raphe nuclei of the brain stem and form a complex network of projections throughout the brain. Many different approaches have been used in the past to investigate the roles of serotonin in brain function. In the current issue, Hainer et al. (DOI: 10.1021/acschemneuro.5b00045) summarize recently developed optogenetic methodologies that allow unprecedented selectivity for manipulating serotonergic neurons in highly spatially and temporally controlled manners. Today, there are numerous genetically modified mouse lines that have been developed for this purpose. This review summarizes the animal models designed to manipulate serotonergic neurons and compares their suitability for specific questions, giving numerous examples of applications.

The current issue also includes Viewpoints from Parrot et al. (DOI: 10.1021/acschemneuro.5b00003) and McElligott (DOI: 10.1021/acschemneuro.5b00081) on approaches to improving optogenetic-driven analysis of neurotransmission. These authors emphasize the need for *in vivo* chemical monitoring to elucidate neurotransmitter dynamics induced by optogenetic manipulations and cautionary perspectives regarding optogenetic activation of interconnected neural circuits.

5-HT$_2$C RECEPTORS IN FOOD AND DRUG REWARD

Impulsivity is a common trait among individuals with various chronic health disorders (e.g., substance use disorder, attention deficit disorder, autism, and obesity/binge eating disorder). In the current issue, four articles focus on the roles of 5-HT$_{2C}$ receptors and the potential of receptor agonists as therapeutics to treat food- and drug-related addictive disorders.

Anastasio et al. (DOI: 10.1021/acschemneuro.5b00094) meld animal models, biochemistry, and pharmacology methods to understand how an imbalance in the serotonin system in the brain contributes to impulsivity. A clearer understanding of the neuromolecular biology of impulsivity is necessary to advance prevention and treatment of addiction and related disorders. In this issue, the authors provide interesting and convincing findings that show that trait motor impulsivity is related to the balance of 5-HT$_{2A}$ to 5-HT$_{2C}$ receptors in the medial prefrontal cortex and that shifting this balance using viral vectors to silence 5-HT$_{2C}$ receptors results in motor impulsivity.

Higgins and Fletcher (DOI: 10.1021/acschemneuro.5b00025) provide a thought-provoking review on the role of 5-HT$_{2C}$ receptors and summarize the failure of current serotonergic drug treatments for substance/alcohol abuse. The authors discuss the therapeutic utility of 5-HT$_{2C}$ receptor agonists for the treatment of impulsive and compulsive disorders, with a focus on feeding behaviors, cocaine use

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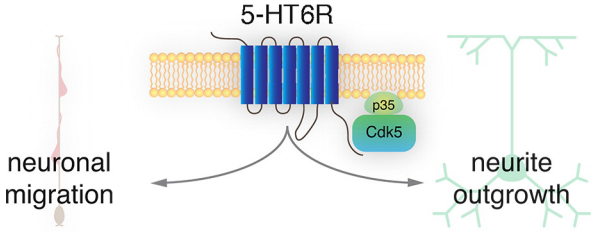
disorder, and chronic nicotine use. They specifically discuss the repurposing of the recently FDA-approved 5-HT_{2C} receptor agonist lorcaserin for these purposes. The authors conclude by discussing the potential development of more selective orthosteric and allosteric ligands for 5-HT_{2C} receptors and their potential therapeutic utility.

In a separate paper, Zeeb et al. (DOI: 10.1021/acschemneuro.5b00017) show that lorcaserin, in addition to acting as an appetite suppressant, directly influences the brain reward pathway through activation of 5-HT_{2C} receptors, likely localized on interneurons in the ventral tegmental area. This article provides insight into the neurobiological mechanism for lorcaserin's ability to increase weight loss in obese individuals and to act as a novel smoking cessation aid.

The ghrelin receptor, GHS-R1a, is well-known for its role in the homeostatic control of food intake and energy balance. Schellekens et al. (DOI: 10.1021/cn500318q) show for the first time that GHS-R1a and 5-HT_{2C} receptors interact to modulate the appetite stimulating effect of ghrelin *in vivo*. The authors demonstrate that the inhibition of 5-HT_{2C} receptor signaling enhances this orexigenic effect. In contrast, the specific 5-HT_{2C} receptor agonist lorcaserin attenuates ghrelin-induced food intake. These results suggest a combined GHS-R1a and 5-HT_{2C} receptor treatment strategy for treating obesity.

5-HT_6 RECEPTOR: AN ORCHESTRATOR OF NEURAL CIRCUIT FORMATION



Serotonin is important in processes such as cognition, emotion, learning, memory, and regulation of food intake and sleep. The activity of serotonergic neurons is strictly regulated by homeostatic mechanisms, including those involving feedback from neurons expressing serotonin receptors. It has recently emerged that among potential targets of early life serotonin, 5-HT_6 receptors (5-HT_6Rs) are an exciting new player. Dayer et al. (DOI: 10.1021/cn500326z) review the diversity of developmental processes and cell types controlled by 5-HT_6Rs during neural circuit formation and their link to neurodevelopmental disorders.

Brouard et al. (DOI: 10.1021/acschemneuro.5b00061) report the effects of 5-HT_6R ligands on the firing of serotonergic neurons. The selective 5-HT_6R agonist WAY-181187 increased 5-HT neuron firing, while the selective 5-HT_6R antagonist SB-399885 reduced 5-HT neuron firing. The nature of 5-HT_6R ligand effects on 5-HT neuronal activity provides novel evidence to suggest the 5-HT_6Rs exert positive feedback control on 5-HT neurons.

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