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Editorial

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Prefrontal Cortex Vistas: A Serotonin Safari

From July 9 to 12, 2014, many of the world's experts in serotonin research journeyed to the Western Cape of South Africa. There, the biennial meeting of the "Serotonin Club", as it is affectionately known, convened near beautiful Hermanus at the Arabella Hotel and Spa. Whales were watched, penguins were spotted, and wine was tasted. Most notably, a stimulating three and a half day program ensued, chaired by Professor Brian Harvey and the local organizing committee. To commemorate the meeting anniversary, *ACS Chemical Neuroscience* is proud to publish this blockbuster issue dedicated to research focused on understanding the diverse physiological roles of serotonin.

If we google "safari", current top hits pertain to the Apple operating system with the same moniker. However, the concept of a safari known to most from childhood evokes expeditions to glimpse the majestic animals of Africa. This special issue of *ACS Chemical Neuroscience* is in essence a "serotonin safari" because it enables sightings of emerging trends in serotonin research. These include a growing appreciation for serotonylation as a post-translational modification, the maturation of a suite of genetically engineered tools to control serotonin transmission with high spatial and temporal precision, and of course, new findings on serotonin's many receptors, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 subtypes.

Articles focused on prefrontal cortex circuitry and serotonergic mediation of cognition, emotion, impulsivity, and stress present the predominant vista. In a review by Mengod et al., precise anatomical locations of 5-HT_{1A} and 5-HT_{2A} heteroreceptors are mapped in rat and primate prefrontal cortex (PFC) and projections to dorsal raphe, ventral tegmental area (VTA), and nucleus accumbens (NAc).[1] This anatomy suggests that serotonin modulates a subset of PFC principal neurons and interneurons. Moreover, information from the PFC is reciprocated to serotonin cell bodies via layer-V 5-HT_{2A}-expressing pyramidal cell-raphe projections. These pyramidal cells also project to the VTA and the NAc. In addition to roles in the mechanisms of antipsychotics, as postulated by the authors, this architecture suggests circuitry by which serotonin regulates reward- and emotion-related behavior via the mesolimbic dopamine system beyond direct serotonergic raphe projections to VTA and NAc. In related work by Leiser et al., the panoply of known serotonin receptor subtypes and their involvement in PFC control of cognitive function is comprehensively reviewed.[2] The point is articulated, via the example of the novel multimodal antidepressant vortioxetine, that serotonergic modulation of cognitive function likely relies on the contextual interplay of multiple PFC serotonin receptor subtypes.

Challis and Berton examine, in depth, the role of the ventromedial prefrontal cortex (vmPFC) in assigning emotional valence.[3] Altered processing of emotionally salient information, particularly toward a more negative bias, constitutes a component of major depressive disorder. The authors synthesize literature supporting this idea with a focus on conditioned social defeat stress as an animal model. These authors conclude that vmPFC control of raphe serotonergic circuits is disturbed in response to defeat stress, while stimulation of the vmPFC, similarly to deep brain stimulation protocols in human patients, restores the function of this circuit and normalizes social affective behavior.

Puig and Gener review evidence for serotonergic modulation of synchronized brain oscillations (coordinated activity of neuronal ensembles) between prefrontal cortex and hippocampus.[4] Again guided by neuroanatomy, interconnections between these regions and with the dorsal and median raphe suggest a role for serotonergic coordination of synchronized interregional activity. Network activity synchronized via theta rhythms occurs during learning and memory and is modulated by dopamine. Nonetheless, research on coordination of neural networks by serotonin neurons during behavior tasks and in the context of brain diseases involving cognitive disruption (e.g., schizophrenia) is lacking and ripe for future investigation. In keeping with the subcontext of serotonin/dopamine interactions, Niederkofler et al. elegantly review and give insights into the parallel and interwoven developmental trajectories of these neurotransmitter systems.[5] They emphasize differential effects on serotonergic arborization in medial prefrontal cortex (mPFC) vs striatum following perinatal loss of dopamine neurons.

Two additional articles highlight prospects on serotonin's functions in the prefrontal cortex. In an article by Anastasio, Cunningham, and co-workers, a finely tuned balance between 5-HT_{2A} and 5-HT_{2C} receptors in mPFC is shown to regulate motor impulsivity, a trait important in substance use disorder and other psychiatric disorders.[6] Schipper, Homberg, and colleagues demonstrate the impact of serotonin transporter (SERT) expression levels on responses to stress controllability.[7] Here, rats lacking SERT were better able to avoid signaled stress and showed differential activation of the mPFC vs the dorsal raphe compared with rats with normal SERT levels.

We hope the *ACS Chemical Neuroscience* readership is inspired by the developments in the field of serotonin research as you navigate your own brain safaris. All are warmly encouraged to attend the *ACS Chemical Neuroscience* cosponsored International Society for Serotonin Research mixer at the upcoming Society for Neuroscience Meeting to be held Monday, October 19, 2015, from 6 to 8 pm at the Highline Bar and Lounge, 169 W Kinzie Street, Chicago, IL. And should you find yourself on your own hunt to understand the neurophysiology of serotonin, we welcome you to attend the 12th International Society for Serotonin Research Meeting, "Serotonin in Seattle", at the Edgewater Hotel July 24−27, 2016 (http://www.serotoninclub.org/index.asp).

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AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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