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Editorial

Thematic Section: Serotonin and Its Receptors

This issue of the Journal focuses on roles of the serotonin system and its receptors in mental illness and treatment responses. The brain serotonin system is implicated in a wide diversity of mood and emotional phenotypes, which raises the question of how a small group of neurons can influence so many processes (Jacobs and Azmitia, 1992). The answer lies in the extensive projections of serotonin neurons throughout the corticolimbic system and the variety of receptor and signaling mechanisms that mediate 5-HT actions at these target areas (Hoyer et al., 2002). The Ohmura (Ohmura et al., 2014) study provides evidence that optogenetic activation in mice of serotonin neurons to increase acutely 5-HT release leads to an immediate increase in anxiety-like behaviour in the elevated plus maze. Interestingly 5-HT release in the ventral hippocampus but not in the striatum, was associated with spatial anxiety. Most interestingly, activation of neurons located in the median but not dorsal raphe increased anxiety, consistent with strong projections of median raphe neurons to prefrontal cortex, amygdala and hippocampus (Bang et al., 2012). While an increase in 5-HT may elicit acute anxiety, acute treatment with SSRI can reverse depression-like phenotype in the forced swim test (FST) (Lucki et al., 2001). Tang et al., compared 4 different mice strains for their immobility time and response to SSRI in the FST and tail suspension test and found a correlation of antidepressant response with levels of 5-HT transporter (5-HTT) protein in ventral hippocampus. These results are consistent with the depressive phenotype and resistance to SSRI treatment that is associated with the 5-HTT s/s genotype in humans and primates that leads to lower levels of 5-HTT expression.

How can we reconcile the differing effects of increased 5-HT activity on anxiety vs. anti-depressant response? This could be due to activity changes in dorsal vs. median raphe and differential activity of these projections in different brain targets such as hippocampus or prefrontal cortex. In addition, the actions of 5-HT depend on the repertoire of receptors expressed on target neurons such as pyramidal vs. interneurons (Albert et al., 2014; Varga et al., 2009). In human subjects, atypical antipsychotics such as quetiapine antagonize 5-HT2A receptors in addition to dopamine-D2 receptors, and have fewer extrapyramidal side effects but are associated with weight gain. Rasmussen et al., found a strong association between the level of cortical 5-HT2A binding potential in antipsychotic naïve first episode schizophrenic patients and the extent of weight gain (average of 5 kg) produced by chronic 6-month quetiapine treatment. This result suggests a key role for 5-HT2A receptors in this adverse effect of quetiapine that may apply to other atypical antipsychotics that target 5-HT2A receptors. 5-HT2C receptors have been implicated in reducing cocaine reinstatement. Pockros-Burgess et al., show that pharmacological activation of 5-HT2C receptors in the central amygdala reduced cocaine reinstatement; while injection in the basolateral amygdala, an area implicated in fear memory, 5-HT2C agonist increased anxiety-like behavior in the elevated plus maze without affecting cocaine reinstatement. These studies show that activation of the same 5-HT receptor within different sub-regions within the same target (amygdala) can have very different behavioral outcomes. This suggests that differential regulation of 5-HT receptors in different brain areas may contribute to different behavioral phenotypes.

In this light, Szewczyk et al., have examined the effects of four different chronic stress paradigms of depression-like behavior including olfactory bulbectomy, chronic mild stress, prenatal stress, and stress during pregnancy, on the levels of 5-HT1A receptors and its known transcriptional regulators (NUDR/Deaf1 and Freud-1) in prefrontal cortex and hippocampus. 5-HT1A receptors were generally down-regulated by stress, but the effect depended on the types of stress and the gender. In some cases, 5-HT1A regulation was compensated for by alterations in transcription factors, in some case it appeared to be driven by an increase in transcription factors, while in the hippocampus 5-HT1A down-regulation appeared to be post-transcriptional at the protein level. These studies illustrate the region and stress dependency of 5-HT receptor regulation that we are only beginning to understand.

In summary, the studies demonstrate and exploit the remarkable brain region specificity of 5-HT projections and cell specificity of 5-HT receptors to modulate different behavioral outcomes. By specifically targeting 5-HT projections or specific 5-HT receptor subtypes or their long-term expression, it may be possible to design better more selective strategies to treat mental illness.

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