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Introduction

The amygdala and the hypothalamus have long been recognized as two critical structures in the expression of emotions and stress-related responses. In a broad sense, the hypothalamus functions as the coordinating site for autonomic, endocrine and behavioral responses, while the amygdala is thought to be the structure that links these responses to subjective stress and emotional experiences. Although this general scheme has been accepted for some time, the specific mechanisms by which these structures are able to express and regulate these complex neural response networks is only now being elucidated. Furthermore, much of the functional data with these brain regions were derived from rodent studies with limited primate or human data. Currently available neuroanatomical, electrophysiological, molecular, pharmacological and neuroimaging tools have dramatically enhanced our ability to study these complex functions within the central nervous system of not only rodents but also primates and humans. With that in mind, the current special issue of *Pharmacology Biochemistry and Behavior* has been put together with two specific goals. The first was to highlight some of the recent advances in our understanding of the functional roles of the amygdala and hypothalamus with review articles summarizing current data relating to specific functions or disease states. The second goal was to provide some original research further elucidating the functional roles of these two structures.

The issue begins with a report by Pitkanen and Kemppainen, comparing the connectivity of the lateral nucleus, the primary site for most afferents to the amygdala, in rodents, primates and humans. Such comparative anatomy is essential to enable us to extrapolate information from lower mammals to human brain function. As evident in this report, there is a substantial conservation of connectivity across species, but also some important differences relating to the predominant sensory cues utilized by the different species. The next report by Walker and Davis reviews the functional role of glutamate neurotransmission in the amygdala utilizing fear-conditioning responses in the startle test. Following this, utilizing another fear-conditioning paradigm, Shinnick-Gallagher and colleagues provide new electrophysiological data suggesting an association between this behavioral learning and increased presynaptic glutamate release as well as some post-synaptic changes in the amygdala. Similar to glutamate-induced excitation, blocking the GABA mediated inhibition in the amygdala can induce fear and anxiety responses. The next report by Thielen and Shekhar presents new data demonstrating the development of conditioned avoidance following amygdala priming with a $GABA_A$ receptor antagonist.

In addition to these classic neurotransmitters, the amygdala contains some of the highest concentrations of neuropeptides. These peptides contribute greatly to the complexities of the functional regulation within the amygdala. The next series of reports provide important new data elucidating the functional roles of these neuromodulators within the amygdala. Morilak and colleagues demonstrate that during stress, excessive activation of norepinephrine induces the release of galanin, a peptide with anti-stress effects, highlighting the built-in protective mechanisms within these limbic circuits. In another report, Sajdyk, Gehlert and colleagues provide new data showing that neuropeptide Y (NPY), a neuromodulator that is often thought to reduce anxiety responses in the amygdala, could have the opposite effect when it acts at the NPY-2 receptors. Leptin, another neuroactive peptide implicated in feeding, and which interacts with NPY, appears to have differing behavioral and neurochemical effects in the hypothalamus and the amygdala, as demonstrated by Thorshell, Heilig and colleagues. While these rodent studies demonstrate the importance of the amygdala in stress responses, the study by Drevets and colleagues extends this to human stress responses and depressive disorders. They provide exciting new data, utilizing positron emission tomography and neuroendocrine measures, demonstrating that depression is associated with increased activation of the amygdala, which correlates with increases in stress induced cortisol release. The review by McDougle and colleagues similarly demonstrates the importance of the amygdala in human social responses and the pathophysiology of social deficit disorders such as autism.

The hypothalamus is the key efferent region for stress related endocrine, behavioral and autonomic responses, and understanding the regulation of these responses by neurons within and outside the hypothalamus is an important step in elucidating the effects of stress on the organism. Therefore, a series of reviews by a number of leading researchers in this area provide the current understanding of stress and defense responses regulated by the hypothalamic nuclei.

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The paraventricular nucleus of the hypothalamus is the site of stress hormone release, and Herman, Tasker, Cullinan and Zigler provide extensive review of the intrinsic regulation of this system. The report by DiMicco and colleagues highlights the importance of the dorsomedial nucleus of the hypothalamus in regulating stress induced autonomic and neuroendocrine responses and its role in regulating the paraventricular nucleus. The report by Canteras demonstrates a selective medial hypothalamic network that may be critical in regulating defensive behaviors such as those elicited by predator exposure. In addition to limbic inputs, these hypothalamic responses are also modulated by the ascending brain stem monoamine pathways. The report by Shekhar and colleagues demonstrates the involvement of the ascending norepinephrine inputs in the "panic-like" responses elicited within the dorsomedial nucleus of the hypothalamus.

Finally, in addition to emotional and stress responses, the amygdala and related structures are recently being recognized to be important in the development and maintenance of drug abuse and dependence. The new data provided by Markou and colleagues demonstrate the involvement of the central nucleus of the amygdala in amphetamine self-administration, and the review by McBride summarizes its role in alcohol abuse and dependence. Lastly, the report by See reviews the evidence suggesting a role for amygdala and related limbic structures in the pathophysiology of drug-seeking behavior and relapse in drug dependent subjects. Thus, the contributions to this issue are both broad and scholarly in their approach to elucidating the functional roles of the amygdala and hypothalamus. It is hoped that this issue will not only provide a breadth of useful knowledge about these structures but also convey the excitement of the advances being made in this area of neuroscience.

Anantha Shekhar
Guest Editor