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Responses to stress: from the periphery to the brain

Editorial overview

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Daniele Piomelli studied Pharmacology and Neuroscience at Columbia University and Rockefeller University in New York. After working at the INSERM in Paris (France) and at the Neurosciences Institute in La Jolla (California), he joined the University of California, Irvine, where he is now Louise Turner Arnold Chair in Neurosciences and a Professor of Pharmacology. His primary research interest is the Biochemistry and Pharmacology of lipid mediators. Author of more than 150 papers and 3 full-length books, Dr Piomelli also serves as the Founding Director of the unit of drug discovery and development at the Italian Institute of Technology in Genoa, Italy.

This issue of the Neuroscience section of Current Opinion in Pharmacology is devoted to reviews describing peripheral and central mechanisms involved in the response to stress, and the therapeutic opportunities such mechanisms can offer. The issue starts at the interface between the external world and the body — where mechanical and chemical stressors are first sensed and reacted to — with a review by Christoph Stein and Leonie Siegel on the roles played by peripheral opioid peptides in the modulation of pain responses. Activated by harmful stimuli, immune cells embedded in skin tissue or derived from blood during tissue injury and infection secrete the peptide beta-endorphin, which acts on opioid receptors located on sensory nerve terminals to reduce neuronal excitability and alleviate both pain and neurogenic inflammatory responses. This is one of the several neural and non-neural processes that strive to counterbalance the effects of pain-inducing and inflammation-inducing signals released by tissue injury. Prominent among the latter is calcitonin-gene-related peptide (CGRP), a neuropeptide expressed in and secreted from pain-sensing neurons, which contributes in important ways to the pathogenesis of migraine headache. Pierangelo Geppetti and collaborators review the natural history of CGRP and its G-protein-coupled receptor, and make a strong case for the use of CGRP receptor antagonists to treat migraine attacks.

Moving from the periphery to the central nervous system (CNS), the reviews by Jerold Chun, Alessandro Guidotti, Shu Narumiya, and Beat Lutz examine four different classes of lipid-derived messengers, which are thought to participate in the response to stimuli that threaten body homeostasis. Chun and coworkers focus on lysophosphatidic acid, outlining both its important roles in neural development and pain, and the still-limited pharmacological toolkit available to study its multiple G-protein-coupled receptors. Guidotti and collaborators present the intriguing hypothesis that increased biosynthesis of neurosteroids in the brain is responsible, at least partly, for the pharmacological effects of fluoxetine and related antidepressant medicines. If confirmed in future studies, this hypothesis would open up new avenues for drug discovery in depression, anxiety, and other stress-related disorders. Unexpected possibilities in these therapeutic areas are also offered by G-protein-coupled receptors that ligate prostaglandins in the CNS. These arachidonic acid derivatives are best known for their contribution to peripheral inflammation, but studies reviewed by Shu Narumiya and colleagues highlight an important role of brain prostaglandins and their receptors in the control of impulsive behavior. Impulsivity has recently emerged as a behavioral marker of the propensity to take addictive drugs, thus it is reasonable to hypothesize that pharmacological agents that modify this personality trait (prostaglandin receptor antagonists?) might provide new treatment strategies for addiction. The interrelated themes of stress and addiction are also a *leitmotif* in Beat Lutz's overview of the brain

endocannabinoid system. He examines the role of endocannabinoid lipids and their receptors in stress-coping and emotional responses, underscoring the value of this signaling system as a source of future therapies for neuropsychiatric disorders. Perhaps less hypothetical, at least for the moment, is the medical potential of drugs that antagonize the actions of the hypothalamic neuropeptides, hypocretins (also called orexins). Indeed, a recent industry-sponsored proof-of-concept study has shown that a hypocretin receptor antagonist can improve sleep efficiency in patients with primary insomnia. Luis de Lecea and collaborators place this clinical finding in its proper biological context, providing a lucid description of the biological properties of the hypocretins and their functions in the regulation of the sleep–wake cycle.

While the first section of this issue of Current Opinion in Pharmacology is centered upon nonclassical neuromodulators involved in the response to stressful stimuli, its second part begins with reviews on two of the most extensively investigated neurotransmitters in the CNS — dopamine and glutamate. Though familiar to experts and beginners alike, these neurotransmitters still reserve many a surprise, as pointed out by Emiliana Borrelli in her review on dopamine D_2 receptors. Her laboratory's work using genetically modified mice vividly illustrates the functional diversity existing between presynaptic and postsynaptic isoforms of the D_2 receptor protein. The next article, by Lori Knackstedt and Peter Kalivas, summarizes current knowledge on the importance of glutamate in the reinstatement of cocaine-seeking behavior, and provides an appropriate link to the last two contributions in this issue, authored by Kent Berridge, Mary-Jeanne Kreek, and their collaborators. Returning to the issue of drug addiction, which was previously touched upon from a molecular perspective, the two reviews dissect critical psychological components of reward and delineate a path toward the clinical resolution of opiate and cocaine addiction, respectively. The translational focus of these thoughtful discussions provides an appropriate ending to this issue of Current Opinion in Pharmacology, which intends not only to stir basic science discussion but also to stimulate new experimental investigations that bridge the animal-to-human gap, which remains the major obstacle in the discovery of neuropsychiatric medicines.