Responses to stress: from the periphery to the brain

Current Opinion in Pharmacology, 9(1)

1471-4892

Piomelli, D

2009-02-01


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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 endo-
cannabinoid lipids and their receptors in stress-coping
and emotional responses, underscoring the value of this
signaling system as a source of future therapies for neu-
ropsychiatric disorders. Perhaps less hypothetical, at least
for the moment, is the medical potential of drugs that
antagonize the actions of the hypothalamic neuropep-
tides, 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 neuromodu-
lators 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 D2 receptors. Her
laboratory’s work using genetically modified mice vividly
illustrates the functional diversity existing between pre-
synaptic and postsynaptic isoforms of the D2 receptor
protein. The next article, by Lori Knackstedt and Peter
Kalivas, summarizes current knowledge on the impor-
tance 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 appro-
priate ending to this issue of Current Opinion in Pharma-
cology, which intends not only to stir basic science
discussion but also to stimulate new experimental inves-
tigations that bridge the animal-to-human gap, which
remains the major obstacle in the discovery of neuro-
psychiatric medicines.