Plenary lecture I

Therapeutic potential of κ opioids

Charles Chavkin

Department of Pharmacology, University of Washington School of Medicine, Seattle WA, 98195-7280 USA

The dynorphins are released by a variety of stimuli including exposure to behavioral stresses, and these neurohormones activate κ opioid receptors (KORs) to orchestrate key components of the stress response. Pharmacological activation of KORs produces analgesic, hypomotoric, anxiogenic, and dysphoric responses and stress-induced release of the endogenous dynorphins results in similar responses. The stress response is largely protective, and individuals with impaired stress responses have high mortality rates. However, sustained exposure to unpredictable stresses (e.g. repeated forced swim, repeated social defeat, or chronic pain) results in depression-like and anxiety-like behaviors in animal models. In addition, chronic stress exposure also increases drug seeking behaviors and reinstatement of extinguished seeking of addictive drugs including cocaine, ethanol and nicotine. Surprisingly, mice pretreated with KOR antagonists (e.g. norBNI) or lacking either the prodynorphin or KOR genes fail to show anxiety-like or dysphoria-like behavioral responses when exposed to stress. Similarly, mice having their dynorphin/KOR systems pharmacologically or genetically disrupted fail to show stress-induced potentiation of drug seeking or reinstatement of extinguished drug seeking. These findings strongly suggest that KOR antagonists may have therapeutic potential in treating stress-induced mood disorders or addiction risk. Recent studies have further demonstrated that the dysphoric response requires activation of p38alpha MAPK by a GRK3/arrestin-dependent pathway following sustained KOR activation, and that p38 activation stimulates serotonin reuptake in serotonergic neurons. These results suggest that the adverse responses to stress are a consequence of a hyposerotonergic state. Evidence supporting these conclusions will be presented.

Acknowledgments:
This research was supported by USPHS grants from the National Institute on Drug Abuse (DA11672, DA20570, DA30074). The author has no conflicts of interest to report, but does disclose that he has provided consulting advice to Eli Lilly, AstraZeneca, Sepracor, Trevena and Adolor Corporations.

Plenary lecture II

Chronic pain: learning from research into the neurobiology of addiction

Stephen P. Hunt

Cell and Developmental Biology, UCL, London. WC1E6BT UK

There are remarkable parallels between the underlying neurobiology of drug addiction and chronic pain states particularly neuropathic pain that arises from damage or disease of the nervous system. Animal models have suggested that the transition from drug taking to drug addiction may be triggered by a breakdown in homeostatic mechanisms controlling the balance between molecular adaptations that either decrease or increase responsiveness to drug. Repeated drug taking results in synaptic changes that sensitize dopaminergic and striatal neurons and this is opposed by up-regulation of molecular networks that damp down increased excitability. Brain Derived Neurotrophic Factor (BDNF) and the X-linked transcriptional repressor methyl CpG binding protein 2 (MeCP2) play key roles in modulating homeostatic networks during the transition to drug addiction.

Chronic pain states can also be regarded as the result of persistent changes in neural circuitry following resolution of the precipitating injury. In pain states it is also possible to identify comparable opposing homeostatic mechanisms and the involvement of similar molecular players essentially to control the level of pain experienced by the organism following injury. The complex up and down regulation of gene expression that supports sensitization of dorsal horn neurons is initially under the control of MeCP2 and this in turn is regulated by descending pathways that originate in the brainstem and are modulated by BDNF. It is likely that the failure of homeostatic regulation, viewed as a failure of neuronal networks to reset following the resolution of an injury, results in the generation of chronic pain states.