Stress and addiction are strongly related conditions that feedback onto each other at several levels. For example, exposure to stressors can cause relapse to abuse of diverse substances with addictive properties. Conversely, withdrawal from drugs of abuse, or even the state of craving in the absence of overt withdrawal, can serve as stressors that produce many of the same physiological effects as observed in the acute stress response. Moreover, stresses associated with drug withdrawal act as negative reinforcers that maintain or even augment addictive behaviors. Just as stress contributes to addiction, substance abuse can alter the neurobiological substrates that underlie the stress response, affecting stress sensitivity or ability to cope with stressors. Finally, the high co-morbidity of substance abuse and stress-related psychiatric disorders, such as post-traumatic stress disorder and depression, underscore the close relationship between stress and addiction and the likelihood of shared mechanisms.

Elucidating circuits, neurotransmitters, intracellular signaling molecules, and genes that underlie the complex relationship between stress and addiction is invaluable for guiding treatments for both drug addiction and stress-related psychiatric disorders. Initial research into this area focused on the biogenic amines dopamine, norepinephrine and serotonin, as interfaces between stress and addiction. However, the discovery that peptides coexist with and/or modulate the activity of biogenic amine and amino acid neurotransmitters expanded the horizon and offered novel potential mechanisms through which stress and addiction may be linked. Our goal was to assemble, in a single special issue, the most contemporary research on the role of brain neuropeptides involved in stress and addiction. Notably, certain neuropeptides have received more attention in this issue than others. Contributions from Shalev et al., Wise and Morales, Valentino et al., and Koob focus on corticotropin-releasing factor (CRF), a molecule that orchestrates the stress response and that has been particularly implicated in stress-induced relapse and the negative reinforcing effects of withdrawal that contribute to drug-seeking behavior. Endogenous opioids are obvious candidates that link stress and addiction. Within this peptide family, recent attention has turned toward the dynorphin-kappa opioid receptor system and its interaction with stress circuitry to promote addictive behaviors and depression as discussed in papers by Bruchas et al. and by Knoll and Carlezon. The recently identified neuropeptide, orexin/hypocretin, is the subject of several papers in this issue. Although initially characterized in arousal, this system has also been recently found to play an important role in primary rewards as well as in responses to conditioned stimuli associated with rewards. Contributions from Lawrence, Sharf et al., Fadel and Burke, Berridge et al., Aston-Jones et al., and Boutrel et al. present evidence for the emerging role for orexin/hypocretin in abuse liability of several different classes of addictive drugs. It is also notable that orexin/hypocretin mediates some effects of stress on addiction behaviors, providing a good example of functional interactions between this system and CRF. The idea that the neuropeptides CRF, dynorphin or orexin/hypocretin interact at critical points to influence stress responses and addictive behavior is emphasized in papers by Van Bockstaele et al., Martin-Fardon et al., and Borgland et al. This special issue also highlights certain peptides for which a role in stress and/or addiction is just emerging. The contribution by Picciotto et al. emphasizes the potential role of galanin in stress responses and addictive behavior through its effects on multiple monoamine systems. In a similar vein, the article by Commons integrates compelling findings for a potential role of Substance P in stress and addiction through interactions with CRF, opioids and the serotonin system. Contributions by Morales-Medina et al. and McGinty et al. focus on novel roles of neuropeptide Y in stress and addiction through interactions with CRF, opioids and the serotonin system. Contributions by Briand and Blendy and by Zhou et al. take us beyond individual peptides to cellular transcription factors and regulation of gene expression to provide examples of how stress-induced plasticity affects reward substrates and, conversely, how the neuroplasticity associated with chronic administration of drugs of abuse has enduring effects on expression of stress-related genes.

Collectively, this special issue organizes the most current knowledge in the field, and hopefully will inspire additional research into brain neuropeptides to better understand and treat addiction and stress-related psychopathology.