Addiction to alcohol and drugs has been conceptualized as a chronically relapsing disorder of compulsive drug seeking and taking that progresses through three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Multiple sources of reinforcement contribute to the motivation to compulsively seek drugs including core elements of positive reinforcement (binge/intoxication stage) and negative reinforcement (withdrawal/negative affect stage) and conditioned reinforcement (preoccupation-anticipation stage). The construct of negative reinforcement can be defined here as drug taking that alleviates a negative emotional state created by drug abstinence. The negative emotional state that drives such negative reinforcement is hypothesized to derive from dysregulation of key neurochemical circuits that form the brain stress systems within the extended amygdala, basal ganglia and frontal cortex. Specific neuroplasticity in these circuits includes not only recruitment of the classic hormonal stress axis mediated by corticotropin-releasing factor (CRF) in the hypothalamus, but also extrahypothalamic CRF in the extended amygdala and frontal cortex. Recruitment of dynorphin-κ opioid aversive systems in the ventral striatum and extended amygdala represents another dynamic neuroplasticity of the brain stress systems. In animal models, acute withdrawal from all major drugs of abuse increases reward thresholds, increases anxiety-like responses, increases extracellular levels of CRF in the central nucleus of the amygdala and increases basal ganglia dynorphin. CRF and kappa receptor antagonists block motivational responses associated with withdrawal, and compulsive-like drug taking during extended access. Excessive drug taking also engages activation of CRF in the medial prefrontal cortex and is accompanied by deficits in executive function that may facilitate the transition to compulsive-like responding and relapse. Thus, compelling evidence exists to argue that plasticity in the brain stress systems, a heretofore largely neglected component of dependence and addiction, is triggered by acute excessive drug intake, is sensitized during repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of addiction. The neuroplasticity of the brain stress systems in addiction not only provides understanding of the neurobiology of negative reinforcement mechanisms in addiction, but also provides key insights into how the brain processes negative emotions.