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Nociceptin/orphanin FQ reverses the escalation of oxycodone self-administration by normalizing GABA transmission in the amygdala in rats with high addiction-like behaviors

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Approximately 25% of patients who are prescribed opioids for chronic pain misuse them, and 5-10% develop an opioid use disorder. Although the neurobiological target of opioids is well known, the cellular mechanisms that are responsible for the development of addiction-like behaviors in some but not all individuals are poorly known. To address this issue, we used a unique outbred strain of rats (Heterogeneous Stock) that mimics the behavioral and genetic diversity that is found in humans and characterized individual differences in addiction-like behaviors using an Addiction Index that incorporates the key criteria of opioid-use disorder: escalated intake, compulsive-like responding, and hyperalgesia. Using *in vitro* electrophysiological recordings in the medial subdivision of the central nucleus of the amygdala (CeA), we found that rats with high addiction-like behaviors (HA) exhibited a significant increase in γ-aminobutyric acid (GABA) transmission compared with rats with low addiction-like behaviors (LA) and naive rats. Superfusion of the CeA slice with nociceptin/orphanin FQ peptide (N/OFQ; 500 nM), an endogenous opioid-like peptide with anti-opioid effects, normalized GABA transmission in HA rats. Intra-CeA levels of N/OFQ were lower in HA rats than in LA rats. Intra-CeA infusions of N/OFQ (1 μg/site) reversed the escalation of oxycodone self-administration in HA rats but not LA rats. These results demonstrate that the downregulation of N/OFQ levels in the CeA may be responsible for hyper-GABAergic tone in the CeA that is observed in individuals who develop addiction-like behaviors. The development of small molecules that target the N/OFQ system may have therapeutic efficacy for the treatment of opioid use disorder.