Dopamine in the Nucleus Accumbens Shell Mediates Acute Opiate Withdrawal  
Sofiya Hupalö 1, Anna K. Radke 2, and Jonathan C. Gewirtz 2,3  
College of Biological Sciences 1, Graduate Program in Neuroscience 2, Department of Neuroscience 3, University of Minnesota, Minneapolis, MN 55455

Background

• The neural events that underlie the transition from initial drug use to compulsive addiction permanently rewires brain reward circuitry. Knowledge of the mechanisms that govern early opiate use is essential to understanding how addiction manifests.

• Addiction is in part driven by the motivation to relieve negative affective symptoms of withdrawal such as anxiety, dysphoria, and irritability. The onset of these symptoms in the early stages of opiate abuse drive negative reinforcement and contribute to subsequent use and dependence.

• Opiates such as morphine increase activity and alter neurotransmission in structures of the extended amygdala circuit, a forebrain macrostructure that receives input from regions associated with stress and reward.4

• Increased extracellular concentrations of dopamine in mesolimbic and extended amygdaloid structures are associated with euphoric, rewarding effects of opiates and other drugs of abuse.5 Decreases in mesolimbic dopamine activity in the nucleus accumbens (NAc) are also associated with opiate abstinence and withdrawal.6,7

• The opponent process theory of addiction asserts that euphoric states produced by drugs are countered by feedback mechanisms that maintain homeostasis by promoting negative affective states.4,8

• This suggests that the neural mechanisms mediating positive reinforcement also regulate negative reinforcement. Indeed, studies show that opiate withdrawal involves decreased mesolimbic dopaminergic activity.4,9,10 Thus, we hypothesized that acute morphine withdrawal induces anxiety when dopamine levels subside after the initial morphine-induced surge.

Results

Apomorphine infusions into the NAc shell, CeA, and dBNST

Figure 1. Consensus targets of the extended amygdala. Bilateral cannulas were placed in the (a) nucleus accumbens shell (NAc) (AP: 7.2 mm, ML: 2.5 mm, DV: −7.9 mm from Bregma); (b) dorsal lateral bed nucleus of the stria terminalis (dBNST) (AP: −6.5 mm, ML: 3.3 mm, DV: −8.8 mm from Bregma); (c) central nucleus of the amygdala (CeA) (AP: −2.5 mm, ML: 3.6 mm, DV: −6.4 mm from Bregma).

Apomorphine in the NAc shell attenuates morphine-induced WPS

Figure 2. Morphine withdrawal-induced anxiety is mediated by dopaminergic activity in the NAc shell. Morphine withdrawal-induced startle potentiation was attenuated by microinjection of apomorphine (5 μg) into the NAc shell (a), but not into the CeA (b) or dBNST (c).

Methods

• Cannulation Surgery: Animals were anesthetized using sodium pentobarbital (75 mg/kg, i.p.). Twenty-two gauge cannulae were bilaterally inserted into the CeA (AP: 2.0 mm, ML: 4.0 mm, DV: −4.4 mm), dBNST (AP: −4.4 mm, ML: 3.3 mm, DV: −4.8 mm), or the NAc shell (AP: 1.7 mm, ML: 2.5 mm, DV: −7.8 mm) relative to Bregma. Correct placement was later confirmed by histological analysis.

• Infusion: Twenty-eight gauge infusion cannulae connected to 5-μl Hamilton syringes were attached to an infusion pump. Morphine sulfate (1 mg), apomorphine (1 mg/kg), or saline was infused in a volume of 0.5 μl over a period of 2 min and held in place for 1 min afterward.

• Withdrawal-potentiated startle (WPS): Animals were exposed to 20 0.5- and 115 dB white noise bursts every 50 s presented in pseudorandom order. Their movement was recorded by measuring compression spring oscillations that connected to an accelerometer, where output voltage was processed by an amplifier and run in Matlab. Two habituation sessions given prior to drug exposure served as baseline measures. On test days animals received a baseline pretreatment (6 hrs) before morphine and a pretreatment 30 min after apomorphine administration (4 hrs).

• Baseline: Baseline pretreatment (6 hrs) before morphine and a pretreatment 30 min after apomorphine administration (4 hrs).

Conclusions

• Administration of a dopamine receptor agonist into the NAc shell when dopamine levels are falling attenuates WPS. No such effects were observed in the CeA or dBNST.

• We show that withdrawal-induced anxiety, which occurs when dopamine levels subside after the initial morphine-induced surge, can be reversed by activation of dopamine receptors in the NAc shell.

• This finding implicates a mechanism for the recruitment of negative emotional states that drive negative reinforcement to motivate drug use.

• The lack of an effect in the CeA and BNST could be due to the presence and interaction with other neurotransmitter systems in these regions. Whereas dopamine levels fall with prolonged morphine intake, norepinephrine activity in the BNST increases.11,12,13,14 Increased activity of corticotropin release factor (CRF) system in the CeA also accompanies and plays a major role in negative affect.

• The CRF and norepinephrine systems may be recruited in response to decreased dopaminergic activity in the extended amygdala during negative affective symptoms of opiate withdrawal.

• Although it has been well documented that mesolimbic dopamine mediates the positive, euphoric effects of opiates, it was previously unknown whether it is also involved in withdrawal. These experiments aimed to elucidate the mechanisms of the early stages of opiate addiction, which is crucial to understanding the neurobiology of drug abuse.

Acknowledgements

This research was funded by the NIH grants T32-HD007154 and DA018784, the University of Minnesota, and the Undergraduate Research Opportunities Program (UROP). Thanks to Jacob Leslie and Kate Reise for the emotional support throughout this project.

References