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Tales from the dark side: Do neuromodulators of drug withdrawal require changes in endocannabinoid tone?

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ABSTRACT

Environmental and interoceptive cues are theorized to serve as 'signals' that motivate drug seeking and effects that may be augmented in the withdrawn state. Phasic dopamine release events are observed in the nucleus accumbens in response to such motivational salient stimuli and are thought to be necessary for drug-associated cues to trigger craving. We recently demonstrated how dopamine neurons encode stimuli conditioned to a negative event, as might occur during conditioned withdrawal, and stimuli predicting the avoidance of negative events, as might occur as an addict seeks out drugs to prevent withdrawal. In this review we first discuss how the subsecond dopamine release events might process conditioned withdrawal and drug seeking driven by negative reinforcement processes within the context of our dopamine data obtained during conditioned avoidance procedures. We next describe how the endocannabinoid system modulates phasic dopamine release events and how it might be harnessed to treat negative affective states in addiction. Specifically, we have demonstrated that endocannabinoids in the ventral tegmentum sculpt cue-induced accumbal surges in dopamine release and, therefore, may also be mobilized during drug withdrawal.

1. Introduction

Negative reinforcers, or events that increase the probability of behavioral actions resulting in the escape or avoidance of the particular event, are thought to play a prominent role in drug addiction. By recruiting neural pathways that process negative reinforcement, drug withdrawal is theorized to produce a negative emotional state—capable of driving persistent drug seeking (Childress et al., 1988; Koob et al., 1998). While traditionally thought to be specific to drugs producing explicit somatic withdrawal symptoms, like opiates and alcohol, it is now recognized that all drugs of abuse produce some form of withdrawal.

1.1. Evidence for drug withdrawal

Drug withdrawal subsists in the absence of overt symptomatology (e.g., delirium tremens). For example, Wood and Lal (1987) used drug-discrimination to demonstrate that cocaine withdrawal is anxiogenic in nature. In their early behavioral pharmacological work, rats were trained to respond on one of two levers for food pellets under an FR10 reinforcement schedule after either receiving injections of the anxiogenic drug pentylenetetrazol or in the absence of any drug effect. They then tested to see whether the subjective effects of cocaine withdrawal generalized to those produced by pentylenetetrazol by treating rats with cocaine (20 mg/kg IP) every 8 h for 7 days, and then assessing lever selection after 8, 24, 96, 120 and 148 h of forced abstinence. They found that the withdrawal effects of cocaine generalized to the pentylenetetrazol stimulus effects, as animals increasingly selected the pentylenetetrazol-paired lever over the first 120 h of abstinence. While this study demonstrated that cocaine withdrawal is anxiogenic in nature, it is important to note that the reported withdrawal effects were devoid of somatic symptoms, such as: diarrhea, wet-dog shakes, weight loss, teeth chattering, tremors and convulsions (Wood and Lal, 1987). Clinical studies corroborated the existence of a cocaine withdrawal syndrome, characterized by anxiety and sleep disturbances (Gawin, 1991; Watson et al., 1992). Another classic example are the cannabinoids (e.g., marijuana), a drug class long thought to be devoid of withdrawal symptoms (Solomon and Corbit, 1974). While spontaneous withdrawal symptoms are difficult to detect in experimental animals (Aceto et al., 1996, 2001), pronounced somatic withdrawal symptoms (e.g., wet dog shakes, paw tremors) are inducible by challenging dependent animals with a cannabinoid CB1 receptor antagonist (Aceto et al., 1995; Tsou et al., 1995). Clinical studies further described a spontaneous cannabis-withdrawal syndrome, characterized by: anxiety, weight loss, restlessness, sleep problems, chills, depressed mood, physical discomfort, shakiness, and sweating (Budney and Hughes, 2006). Together, these preclinical and clinical reports indicate that the majority of abused drugs are capable of producing some form of withdrawal.

Abbreviations: 2AG, 2-arachidonoyl-glycerol; DA, dopamine; DG, Diacylglycerol; DGL, diacylglycerol lipase; GABA, gamma amino butyric acid; Glu, glutamate; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-Aspartate Receptor; PLC, phospholipase C.

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1.2. Conditioned withdrawal

Through Pavlovian conditioning, interoceptive (e.g., subjective effects) and exteroceptive (e.g., sights, sounds, smells or situations) cues become associated with withdrawal symptoms and act cumulatively to motivate drug seeking. Indeed, conditioned withdrawal is such a strong force in drug addiction, it was one of the earliest factors noted by the medical community (Wikler, 1973) and continues to be considered a critical feature in addiction by today's leading psychiatrists (O'Brien et al., 2009).

2. Conditioned withdrawal: interoceptive effects

Subjective effects produced by drug withdrawal increase over periods of abstinence (Wood and Lal, 1987) and may contribute to the increased drug seeking ('incubation') that is observed over a course of weeks in reinstatement self-administration models of addiction (Grimm et al., 2001; Lu et al., 2004; Tran-Nguyen et al., 1998). Consistent with this supposition, Wang et al. (2013) recently reported that the conditioned peripheral effects of cocaine are sufficient to increase drug seeking over time in rats withdrawn from cocaine (Wang et al., 2013). It has been theorized that these conditioned interoceptive drug effects and negative affect play off of each other to produce even stronger motivational influences on drug craving (Baker et al., 2004; Childress et al., 1988). The concept that negative affect itself conjures up withdrawal symptoms and produces drug craving is supported by studies involving hypnotically induced states of depression. In these studies it was found that hypnotically inducing a state of depression in detoxified drug addicts led to the emergence of conditioned withdrawal symptoms and drug craving (Childress et al., 1987, 1994).

2.1. Conditioned withdrawal: exteroceptive effects

Withdrawal associated exteroceptive cues also play a prominent role in the addiction phenomenon. Extensive clinical studies demonstrating the power withdrawal associated exteroceptive cues hold over drug craving and drug seeking exist (Childress et al., 1986a, 1986b, 1988; O'Brien, 1975; O'Brien et al., 1977). Recent advances in neuroimaging have allowed experimenters to expand upon these initial behavioral and physiological observations to indentify the neural substrates involved in cue-induced drug craving (Childress et al., 1999; Volkow et al., 2006, 2008). Of note, these studies demonstrate that rapid surges in dopamine release within the striatum are necessary for drug-associated cues to trigger craving (Volkow et al., 2008).

3. Relating conditioned avoidance to conditioned withdrawal

We recently demonstrated that rapid surges in dopamine release within the ventral striatum encode stimuli during conditioned avoidance (Oleson et al., 2012a) and believe these data provide novel insight into how the brain processes conditioned withdrawal. The parallels between this signaled footshock avoidance procedure and conditioned withdrawal have been described in detail elsewhere (Baker et al., 2004). Briefly, Baker and colleagues recognized that conditioned avoidance exemplifies the sort of motivational processes that are theorized to motivate addictive behavior during drug withdrawal and further point out that conditioned avoidance incorporates the primary elements involved in conditioned withdrawal—namely exteroceptive cues (e.g., warning signals indicate that shock is avoidable) and subjective responses (e.g., negative affective state; fear).

3.1. Conditioned avoidance methodology

To investigate whether dopamine encodes cues during conditioned avoidance, we used fast-scan cyclic voltammetry to measure dopamine concentration transients in the ventral striatum (specifically the nucleus accumbens core) while rats behaved in an operant signaled foot shock avoidance procedure. In this task, a cue light was presented as a warning signal for 2 s prior to the delivery of recurring foot shocks. During this 2-s warning period, a response lever extended into the operant chamber which, if depressed, produced a 20-s safety period signaled by a tone. Rats initiated an avoidance response by pressing the lever within the 2-s warning period, thus entirely preventing shock. Alternatively, rats initiated an escape response by pressing the lever after shocks commenced, thus terminating ongoing shock. This experimental design allowed us to assess dopamine signaling during warning signal presentation, safety periods and during two distinct behavioral responses—avoidance and escape. Animals received extensive training (~15–25 sessions) and exhibited >50% avoidance before recording sessions commenced.

3.2. Conditioned avoidance and dopamine

We (Oleson et al., 2012a) found that dopamine concentration transients rapidly increased upon presentation of the warning signal (Fig. 1A, first peak) in a manner that predicted when animals successfully avoided foot shock, as the concentration of cue-evoked dopamine release remained significantly higher in avoidance versus escape trials. We also observed rapid increase in dopamine concentration transients during the safety period (Fig. 1B, second peak). These data demonstrate that subsecond dopamine release accompanies cues predicting negative reinforcement. Regarding a parallel to the addiction phenomenon, as previously suggested (Baker et al., 2004), we infer that dopamine neurons encode the warning signal similar to an environmental cue directing an animal toward the relief of withdrawal (i.e., drug availability)

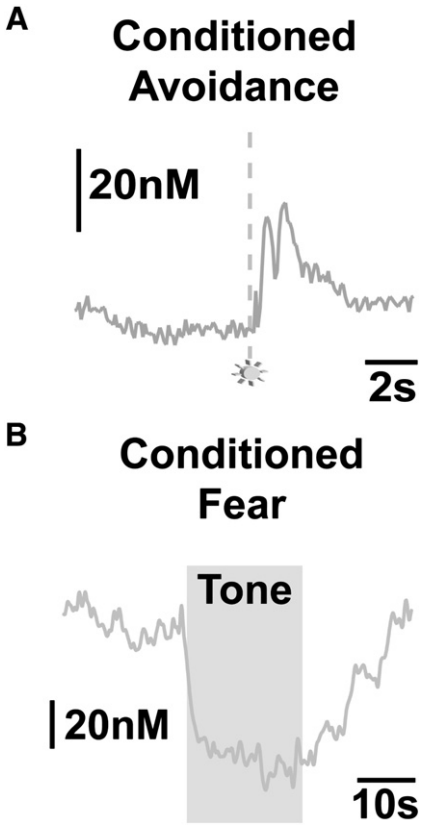

Fig. 1. A) Dopamine encodes conditioned stimuli during an avoidance response. The dopamine concentration trace is centered on warning signal presentation (represented by dashed line with light) and plotted as a function of time. B) Dopamine encodes conditioned stimuli during a fear response. The dopamine concentration trace is centered on tone presentation (gray bar) and plotted as a function of time.