Social Stress Modulations of Accumbal Dopamine during Extended Cocaine Binge

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Abstract

Rationale: Increased vulnerability to drug abuse, specifically cocaine abuse, is associated with repeated exposure to stressful events, both in clinical populations and in animal models of drug abuse. Stressful experiences are hypothesized to induce long term neuroadaptations within dopamine rich circuitry which influences physiological and behavioral response to drug exposure.

Objective: To examine factors that contribute to the maintenance and termination of extended bouts of cocaine intake, and the extent to which altered dopaminergic response to cocaine may promote sustained bingeing in defeat-experienced rats.

Methods: Male Long-Evans rats were subjected to 4 episodes of social defeat stress intermittently over the course of 10 days. Following exposure animals were implanted with intravenous catheters and microdialysis cannula targeting the nucleus accumbens shell (NAc Shell). After recovery, animals were trained to self-administer cocaine (FR1 → FR5; 0.75 mg/kg per infusion). Once stable levels of responding were established, animals were given an unlimited access to "binge" (FR5; 0.3 mg/kg per infusion) over 24 hours during which microdialysis was conducted to measure extracellular dopamine (DA) in the NAc. Shortly after completion of the "binge", a cocaine challenge was administered (1.0 mg/kg I.V.) to assess dopaminergic response to cocaine after prolonged drug exposure.

Results: The defeat experienced animal (n=1) displayed a lower baseline DA tone, and exhibited a larger relative increase in dopamine during self-administration. This animal also responded at higher rates and for a longer duration than controls (n=4) throughout the unlimited access "binge". Upon termination of self-administration, all rats displayed a pronounced reduction in accumbens DA. Where this was prolonged in control rats, baseline DA levels were restored most quickly in the defeat-experienced rats. Interestingly, after extended self-administration, acute cocaine challenge did not elicit increased extracellular DA in non-stressed rats, while defeat-experienced animals displayed intact dopaminergic response to drug (300% increase from baseline).

Conclusions: These preliminary data offer some insight into potential stress induced differences in mesolimbic DA transmission during extended cocaine binge. Disparity in tonic extracellular DA lends some support to the DA deficiency hypothesis of addiction. However, defeat-experienced animals may also retain DA terminal function following prolonged cocaine exposure, which may facilitate extended bouts of self-administration. Further research is necessary to clarify these potential mechanisms by which stress experience potentiates escalated drug use, and perhaps, a vulnerability towards cocaine use disorder.

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Perspectives on Cocaine

The health risks for the stimulant cocaine are numerous, and it is the illegal drug most associated with visits to emergency departments and clinics in the United States, representing 40.3% of visits in 2011 (Substance Abuse and Mental Health Services Administration, 2013). Despite the significance of treating cocaine addiction and cocaine use disorder, no biological mechanism has been identified as a target for treatment. In 2016, worldwide use of cocaine was estimated at 18.2 million people, representing approximately 0.4% of the global population aged 15-64, with the highest regional use present in North America, where approximately 1.4% of people older than 14 (5.1 million people) have used cocaine (United Nations Office on Drugs and Crime, 2016).

Cocaine is a naturally occurring tropane ester alkaloid that is found in the Andes Mountains of South America in the leaves of the Erthroxylum Coca plant (Karch, 2006). Indigenous peoples of South America chewed the leaves for their stimulant effects, and tinctures and extractions from the plant were used in medicinal practices and as a performance enhancer in Europe starting in the mid-19th century (Karch, 2006). The drug cocaine was extracted from the natural source in 1855 and was sold commercially in a variety of medicinal and consumer products such as Coca-Cola, which removed cocaine from its ingredients in 1904. Cocaine containing products were found in the United States until it was banned in 1914 as part of the Harrison Narcotics Act (Johanson, 1986; Karch, 2006). The Controlled Substances Act Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 classifies cocaine as a Schedule II medication, indicating both its high potential for abuse and its limited use in medicinal settings as a local anesthetic (United States of America, 1996).

Cocaine Use and Use Disorder

Despite its medicinal uses, cocaine is more commonly used as a stimulant, and is treated as a narcotic by federal drug control laws and the United States Justice System (C. B. Schultz, 1983). As a member of the stimulant class of drugs, the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) classifies cocaine as capable of causing substance-related use disorders (American

Psychiatric Association, 2013). In the United States most cocaine users are urban dwelling males aged 15 to 35, although women represent 51.5% of users aged 18-25 (Administration Substance Abuse & Mental Health Services, 2005). Of all cocaine users in the United States, 18.6% are estimated to meet the DSM-V diagnostic criteria for cocaine use disorder (Substance Abuse and Mental Health Services Administration & Center for Behavioural Health Statistics and Quality, 2015). Unlike other commonly abused drugs, such as alcohol and nicotine, cocaine is rarely used regularly as most users follow a binge pattern of consumption (Myers et al., 1995). Binge consumption is characterized by short periods of heavy use, such as on paydays or weekends, followed by long periods of little or no drug use, and may be initiated by a stressful encounter or situation (Myers et al., 1995). Controlled consumption on a binge schedule can develop into an overwhelming urge to use cocaine, a characteristic of cocaine use disorder.

In humans, cocaine use disorder is defined as a disorder with a high percentage of relapse, due to the escalating effects of repeated cocaine use, and the resistance cocaine seeking behavior has to adverse consequences such as by extinction and punishment procedures (Gancarz-Kausch, Adank, & Dietz, 2014). Cocaine use disorder is defined by the presence of symptoms that indicate loss of control over drug intake, decreased variety in behavioral responses to cocaine administration, and increased desire or "wanting" to consume cocaine (American Psychiatric Association, 2013; Jaffe, 1990; World Health Organization, 1990). However, there are no cognitive or biological markers identified that are unique to addiction. As such, descriptions of addiction and cocaine use disorder are based on behavioral indicators and are similar to the descriptors used throughout the 20th century (Wise & Koob, 2014). Many theories have been posited to explain the shift from impulsivity to compulsivity common in substance abuse disorders, such as alternative negative reinforcement, opponent process, and incentive-sensitization theories (Koob & Le Moal, 2008; Koob, et al., 1997; Robinson & Berridge, 1993).

It has also been shown that while high reactivity to novel stimuli is related to the propensity to start cocaine self-administration, high impulsivity (as measured by premature responding in a behavioral protocol) predicts the development of addiction-like behavior (Belin et al., 2008). Of these theories, the incentive-sensitization theory may have particular relevance to cocaine use disorder and other stimulant use disorders (Sofuoglu et al., 2003). This theory accentuates the designation of motivational value to cues associated with reward, represented by cocaine for individuals with cocaine use disorder (Robinson & Berridge, 1993). Repeated administration of cocaine causes progressive and lasting neuroadaptations to reward pathways, resulting in sensitization, a progressive increase of the drug's effects with repeated administration. Sensitization causes the neural system to become hypersensitive to stimuli, mediating the process of incentive motivation and enhancing the attribution of incentive salience to experiences and representations of cocaine and cocaine related stimuli. Activation of the mesolimbic dopamine pathway by this process is thought to control the experience of "wanting" and the increased motivational aspects of a drug-associated stimuli (Robinson & Berridge, 1993).

Sensitization to Cocaine

There are a number of factors that influence the sensitization effects of cocaine. Sensitization is dose-dependent, where the greater sensitization follows greater cocaine concentrations, time dependent, with the effects of sensitization increasing with time, and is most robust when cocaine doses are administered or earned intermittently with significant time between injections (Antelman, 1988; Browman, Badiani, & Robinson, 1998). Evidence of sensitization is more easily identified after extended periods of withdrawal, following discontinuation of cocaine taking (Antelman, 1988). Sensitization is also notable for the persistence of neurobiological and behavioral changes that occur. Following the appearance of sensitization, hypersensitivity to psychomotor effects of cocaine remain for months or years after cocaine self-administration has stopped (Paulson, Camp, & Robinson, 1991).

However, sensitization varies significantly among individuals, due to genetic, hormonal, and experiential factors. Psychomotor sensitization has been shown to be strongly linked to strain differences in both mouse and rat models and sex differences, attenuated by castration of males, are also evident (Robinson, 1988; Shuster, Yu, & Bates, 1977). This variability may factor into the variability in susceptibility to addiction observed in human cocaine takers (Robinson & Berridge, 2000). An important note regarding sensitization is that it may not ever occur following repeated cocaine exposure, as it is mediated by learning of conditioned behaviors, and the experimental conditions of drug administration (Robinson et al., 1998). Sensitization is "context-specific" which means that only animals treated with cocaine in the test environment show sensitization after repeated administration (Badiani, Anagnostaras, & Robinson, 1995; Robinson et al., 1998). The presence, or lack, of drug linked contextual cues may factor in the development of sensitization, and cocaine seeing behavior.

In individuals diagnosed with cocaine-use disorder, the process of escalation from occasional to uncontrollable use is not well studied, as the representative population is relatively small and difficult to isolate for analysis, and because the process of neural changes underlying the transition can be slow (Griffin et al., 1989). Currently, there are no comprehensive animal models of cocaine use disorder, as it is difficult to accurately represent the slow changes in use that are seen in human users. To approximate the behaviors observed in humans, models of self-administration on a binge schedule are used (Markou & Koob, 1991). Experiments using the sensitization effects of long duration cocaine binge protocols in animal models may have translational value to humans, as the clinical literature indicates repeated exposure to cocaine may cause the observed increase in psychotomimetic effects, which lasts for significant periods of time, even when experiencing withdrawal symptoms (Segal & Schuckit, 1983). Despite the similarities in behavioral patterns between animal binging models and

humans with cocaine use disorder, the incentive sensitization theory of substance abuse disorders is not sufficient to explain why some humans will take cocaine without being sensitized.

Intravenous Administration of Cocaine

Cocaine is frequently administered via intravenous injections by individuals with cocaine use disorder (United Nations Office on Drugs and Crime, 2016). Intravenous administration has a number of benefits as a drug administration pathway, including shortened onset for drug effects, as well as increased bioavailability and efficacy. When injected into peripheral veins, cocaine users experience the "high" as quickly as 15 to 30 seconds following administration, significantly faster than other common methods such as snorting (3 to 5 minute time course) (Baciewicz, 2017). Intravenous administration of cocaine also produces more pronounced symptoms, as this administration method bypasses first-pass elimination. First-pass elimination is the process of metabolism that decreases the efficacy of medications and drugs by exposure to enzymes present in the body, particularly in the intestine walls and liver, but also present in the vascular endothelium and lungs. When drugs are administered orally or via inhalation, a series of metabolic enzymes interact with the compound, breaking down the active chemical structures and decreasing the bioavailability of the drug. Intravenous administration bypasses many of the sites for first-pass elimination, allowing greater effects to be experienced with lesser doses of cocaine, an attractive concept for users (Pond & Tozer, 1984). This method of administration also poses significant risks to cocaine users. Although hypodermic needles and syringes, the tools necessary for intravenous injections, were readily available in the twentieth century, numerous states have developed legislation limiting or preventing the sale of these items without a prescription, in an effort to crack down on illegal drug use (Baciewicz, 2017). Due to increased scarcity, users may feel pressured to share needles or syringes which, in combination with non-sterile preparation and injection techniques, greatly increases the risks of developing bloodborne pathogens, diseases, and infections. Repeated injections can cause bruising, scarring,

swelling and inflammation of tissue and arteries, necrosis of surrounding tissue, and life-threatening conditions such as thrombosis, embolism, bacteraemia, gangrene, and HIV (World Health Organization, 2009). Regardless of the potential health concerns, intravenous administration is a frequently used cocaine administration route in humans, and therefore has high translational validity to animal models.

Patterns of Cocaine Use in Animal Models

Analysis of behavioral patterns of cocaine usage in non-human primates and rodents has identified patterns and rates of responding for drug usage. In animal models of drug use, self-administration of cocaine is highly behaviorally reinforcing, especially when administered intravenously (Balster & Schuster, 1973; Deneau, Yanagita, & Seevers, 1969). As early as 1968, intravenous administration of cocaine was found to be sufficient to reinforce operant responding in rats when delivered contingently upon completion of the behavioral demand. This responding was highly selective for cocaine administration and remained even if the active lever was changed during the test (Pickens & Thompson, 1968). Rhesus monkeys given access to a fixed ratio schedule of cocaine reinforcement (FR1) showed stable responding across significant time periods, indicating that the reinforcing effects of cocaine are resistant to forming tolerance (Wilson, Hitomi, & Schuster, 1971). Additionally, Balster and Schuster in 1973 demonstrated that when cocaine reinforcement was limited to a nine minute fixed interval (FI9) schedule with a fifteen minute timeout period, the rate of response on the active lever accelerated over the course of the interval and increased with repeated exposure to the FI schedule (Balster & Schuster, 1973; Dews, 1978). Through examination of progressive ratio (PR) schedules of reinforcement, a direct relationship between cocaine dose and break point was established, with animals responding thousands of times for high doses of drug (0.48 mg/kg) (Hodos, 1961; Yanagita, 1973). Additionally, rodents trained on intermittent access schedules

of intravenous self-administration to cocaine mimic behavioral patterns of use similar to those found in recreational users (Balster & Schuster, 1973; Johanson & Fischman, 1989; Weeks, 1962).

Animal models of cocaine use indicate a shift in consummatory behavior, similar to that observed in human users. A single prolonged binge session has been seen to promote changes in cocaine consumption and seeking, promoting future use and increased rates of responding in future binge sessions (Markou & Koob, 1991; Post, 1975). Like humans, animals also experience significant withdrawal symptoms following termination of cocaine binge sessions, which frequently consist of changes in affect that additionally promotes continuation of drug use (Markou & Koob, 1991). Withdrawal is difficult to observe in animal models as anxiety-like behaviors are not easily isolated, but ultrasonic vocalizations and startle responses have been used as measures of these behavioral characteristics. Rats trained on a FR5 for intravenous administration of 0.25mg/infusion cocaine with unlimited access across 12- or 48-hour binge sessions. All experimental animals showed heightened ultrasonic vocalizations and startle responses as soon as 6 hours following termination of the binge protocol, indicating that cocaine use and subsequent withdrawal is sufficient to mediate neurochemical and neurobiological changes that enhance anxiety-like and drug seeking behaviors (Mutschler & Miczek, 1998).

When animals are permitted to self-administer cocaine continuously, responding is initially highest during the entrained active phase of the day/night cycle. After several days of free access self-administration, the circadian controlled patterns of administration become dysregulated as cocaine disrupts neurotransmission (Deneau et al., 1969; Fitch & Roberts, 1993). Early into a 72-hour binge access protocol in rats, autonomic activities were elevated, with decreased variability in intra-infusion time and significant decreases in characteristic circadian rhythmicity. The changes in autonomic circadian rhythms last for more than 2 weeks following termination of cocaine taking (Tornatzky & Miczek, 2000). A new pattern of self-administration emerges after the first few days, involving periods

of extremely high responding interspersed with periods of time where no responses are taken (Bozarth and Wise, 1985). Usage of these continuous access protocols in rodent models of cocaine self-administration provide a viable model for human binge behavior and intake during dependent periods (Markou & Koob, 1991; Segal & Geyer, 1985).

Cocaine self-administering rats will engage in patterns of behavior similar to those seen in human users' binge cycles. If the animals are given unlimited access to cocaine injections, they will often respond with such intensity that they lethally overdose (Bozarth & Wise, 1985). In contrast, self-administration on an intermittent, binge-style schedule is a standard for examining the escalation from recreational to compulsive cocaine use, as this administration method produces neurobiological and behavioral changes most like those seen in humans with cocaine use disorder (Porrino, 1993). When self-administration sessions have short inter-trial intervals (ITIs) and the dosage is high, animals administer in characteristic binge patterns (Roberts et al., 2002). However, decreasing dosage or increasing ITI length causes cocaine intake to become more circadian in pattern. The research surrounding the contingent conditions for rodent binge models suggest that a binge is not normally sustained, and that rodents naturally consume cocaine on a circadian pattern (Roberts, Morgan, & Liu, 2007).

Behavioral and neural effects of prolonged cocaine self-administration access emerge starting around twelve to sixteen hours when cocaine is provided at dose from 0.25-1.5mg/kg per infusion. Response rates in rats under these conditions are highly stable and predictable, and this significant drug intake produces changes in nucleus accumbens biogenic amine (dopamine and serotonin) concentrations that are markedly different than what is observed under limited access conditions (Mutschler, Covington, & Miczek, 2001; Parsons, Koob, & Weiss, 1995; Weiss et al., 1992; Weiss et al., 1992b). During the long access time period, concentrations of dopamine and serotonin noticeably increase and become stable. The increase is significant when compared to baseline, measured before

binge behavior is initiated (Parsons et al., 1995; Weiss et al., 1992). Analyses of the concentrations of serotonin and dopamine in the nucleus accumbens of self-administering rats determined that the concentration of both monoamines increased by approximately 340% of baseline throughout a sustained binge. Under withdrawal conditions, concentrations of both dopamine and serotonin decreased significantly and remained low for more than 12 hours in withdrawal. This change was only seen in animals under binge protocols, and concentrations of monoamines were significantly lower in binging animals than in cocaine naïve or intermittent access animals (Parsons et al., 1995).

Rats given unrestricted access to cocaine on an FR5 schedule of reinforcement for 26 or 72 hours displayed distinctive patterns of cocaine self-administration. The behavioral patterns were noted to fall into distinct phases, observed to be a primary loading phase, a stable responding period with predictable inter-infusion intervals which lasted 8 to 10 hours, a period of increasing variability in inter-infusion intervals emerging between 22 and 24 hours of access (Tornatzky & Miczek, 2000). However, shortly after the termination of prolonged 12-hour binge behavior (i.e. within an hour) levels of both amines decrease significantly below baseline and maintain the new, lowered levels for at least 6 hours after binge secession (Parsons et al., 1995; Weiss et al., 1992). This decrease corresponds to the onset and interval of affective disturbances that emerge during withdrawal from binge cocaine levels, such as anhedonic, depressive-like, and anxiogenic symptoms (Markou & Koob, 1991). Data from studies involving intra-cranial self-stimulation (ICSS) and measurements of ultrasonic vocalizations support the theory that these negative affective symptoms act as additional promotion of drug-seeking behavior, perpetuating binge and addiction behaviors (Markou & Koob, 1991). Despite potential limitations, animal binge models provide a method of analysis for the behavioral patterns commonly seen in humans with cocaine use disorder, and therefore permit analysis of neural pathways underlying and potential treatment options for cocaine use disorder.

Limbic System and Nucleus Accumbens

The biological effects of cocaine act primarily on the limbic system, the collection of structures that supports neural functions of emotion, motivation, and long-term memory (Davidson, 2003). This neural system is distinguished from surrounding brain areas by the relative paucity of short cell axons, the termination of the afferent plexus in the superficial layers, and the absence or poor development of the supragranular layers (MacLean, 1955). The primary structures within the limbic system are the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, cingulate gyrus, and nucleus accumbens (NAc) (Alheid, 2003; MacLean, 1955; Nauta et al., 1978; Zahm, 1998). The NAc is a major component of the ventral striatum and has been implicated in mediating motivational effects, the limbic-motor interface, and the effects of psychoactive drugs, such as cocaine (Salgado & Kaplitt, 2015). In 1904, Ziehen first used the term "nucleus accumbens septi' although the region was described as early as 1872 (Salgado & Kaplitt, 2015). Although the classification of the NAc as a part of the striatum was historically contested, the results of many studies indicated similarities in enzyme histochemistry, opiate receptor distribution, dopamine levels, and neural connections between this region and the rest of the striatum (Herkenham & Pert, 1981; Murrin, Galen, & Kuhar, 1979; Nauta et al., 1978; Parent & Olivier, 1970; Swanson & Cwan, 1975). Nicotinic acetylcholine receptors (nAChRs) on striatal DA terminals regulate striatal DA signaling, and muscarinic acetylcholine receptors (mAChRs) modulate endogenous activity of AChRs and DA terminals, connecting the NAc with other striatal regions (Bolam, Wainer, & Smith, 1984; Foster et al., 2014; Jones, Bolam, & Wonnacott, 2001; Threlfell et al., 2010). γ -Aminobutyric acid type B ($GABA_B$) receptors are expressed in the VTA and NAc, where they play a role in modulating DA release (Bowery, Hudson, & Price, 1987; Xi et al., 2003).

The NAc is located anterior to the anterior commissure and is symmetrical across the midline, and is divided into a central core and outer shell, which surrounds the core medially, ventrally, and

laterally (Johnston, 1913, 1923; Neto et al., 2008). These areas are distinct in many experimental criteria, including histochemical, electrophysiological, cellular, and connectional differences (Wright & Groenewegen, 1996). In humans, the NAc core contains a low density of impregnated neurons and multipolar neurons, consisting primarily of pyramidal-like neurons with spines on secondary branches, while the shell has a high cell density of multipolar and fusiform neurons (Sazdanovic et al., 2011). In contrast, morphological studies of the NAc of rats suggest that the shell has smaller cells with fewer dendrites and spines than the core (Meredith et al., 1992; Meredith, Blank, & Groenewegen, 1989).

The NAc also has differences in the distribution of receptors and neuroactive substances, primarily dopamine, serotonin, and serotonin receptors, with preferential expression in the shell over the core (Deutch & Cameron, 1992; Patel et al., 1995). The NAc is thought to receive indirect inputs from the mesolimbic dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra, and direct inputs from glutamatergic projections from the amygdala, PFC, and other striatal structures (Gorelova & Yang, 1996; Mogenson, Jones, & Yim, 1980; Phillipson & Griffiths, 1985). Medium spiny neurons project from the NAc to areas within the mesencephalon, basal ganglia, and pallidal complex with additional projections to the amygdala and septum (Heimer & Alheid, 1991; Nauta et al., 1978; Swanson & Cwan, 1975; Williams, Crossman, & Slater, 1977). The projections to and from the NAc form networked connections within the neuronal framework, showing a general pattern along the cortico-striato-pallido-thalamo-cortical loop (Alexander & Crutcher, 1990). NAc projections play a major role in the anterior cingulate circuit, which is thought to play a key role in feeding behavior, other motivated behavior, and addiction (Kelley et al., 2005). Significant experimental evidence demonstrates the role of dopaminergic neurons within the NAc in mediating natural reward systems, and the escalation of rewarded behavior into addictive behavior. The mesolimbic DA pathway extends from the VTA and extensively innervates the NAc shell, indicating the role of the NAc in reward circuitry and processing (Berlanga et al., 2003; Groenewegen et al.,

1987). There is debate regarding the relative basal concentrations of the NAc core and shell, but it is known that the shell contains more DA receptors while the core has greater DA utilization and contains more DA transporters (Deutch & Cameron, 1992; Kalivas & Duffy, 1995; Le Moine & Bloch, 1995).

Several areas of the limbic system are thought to be associated with the brain's reward pathway, activation of which is implicated in drug use disorders, including cocaine use disorder. Specifically, the hippocampus' role in memory and learning, and the amygdala's role in emotional responses are factors in the shift from recreational cocaine use to uncontrollable taking (Everitt & Robbins, 2005; Powledge, 1999). The mesolimbic DA pathway, extending from the VTA to regions within the limbic system, is activated by the administration of cocaine, which increases extracellular DA levels, triggering pleasurable experiences, conditioned motivational states of "wanting" or "craving," and causing the drug associated cues (location of drug use, paraphernalia used in administration, etc.) to become reinforcing (Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984). In experimental models, drug cues can act both as a trigger for drug use and as a reinforcer for actions that result in the stimulating effects of cocaine (O'Brien et al., 1990). However, individuals with cocaine use disorder frequently exhibit cocaine seeking behaviors following presentation of a drug associated cue. This is due to the cues' initiatory effects on conditional motivational arousal, making drug seeking more probable through both implicit and explicit means (Bindra, 1978; Carter & Tiffany, 1999; Ehrman et al., 1992; Fischman, 1989; Fischman & Foltin, 1992; Stewart et al., 1984). Examinations of cocaine cue evoked conditioned motivation are limited, as craving cannot be directly measured except through verbal report. Historically, conditioned motivation measured through Pavlovian to instrumental transfer procedures has failed to be elicited by drug cues, but research conducted by LeBlanc et al. in 2012 successfully indicated that noncontingent presentation of cocaine cues would enhance ongoing self-administration behavior (Estes, 1943; Estes, 1948; LeBlanc, Ostlund, & Maidment, 2012).

Biological and Neural Effects of Cocaine

The long and short-term effects of cocaine vary significantly, due to modifications to neural systems that occur following continued cocaine administration. Quickly following cocaine administration, the user experiences increases in heart rate, blood pressure, and locomotor activity, appetite is reduced, and the site of administration is numbed from the drug's anesthetic effects. Cocaine's rewarding effects are produced by the increase in extracellular DA concentrations that emerge once the compound reaches the brain (Ritz et al., 1987). In drug free conditions, stimulation of the limbic system and reward pathways initiates DA release from dopaminergic neurons. Within these neurons, DA is stored in synaptic vesicles until stimulation by action potentials causes the vesicles to join with the cell membrane and release the neurotransmitter into the synaptic cleft and extracellular space, increasing extracellular concentrations. Following release into the synapse DA binds to DA receptors, which may be postsynaptic receptors located on other dendrites, or presynaptic autoreceptors located on the axon terminals of the releasing neuron. High concentrations of DA binding to autoreceptors triggers reuptake mechanisms to maintain stable levels of the amine in the extracellular space. The dopamine transporter protein (DAT) is the primary mechanism by which DA is reabsorbed into the presynaptic neuron. DAT is an integral membrane protein that moves DA across the cell membrane by coupling the transfer to the movement of sodium ions from areas of high concentration within the neuron to areas of low concentration in the extracellular space. The movement of sodium ions is energetically favorable, providing the energy necessary for DA to cross the cell membrane. Cocaine binds directly to DAT, reducing the rate of transport by occupying the transporter's active site and blocking movement of DA across the cell membrane (Church, Justice, & Byrd, 1987; Maisonneuve, Ho, & Kreek, 1995; Maisonneuve & Kreek, 1994).

These short-term actions of cocaine are not sufficient to explain "craving" behaviors and the high propensity for relapse experienced by individuals with cocaine use disorder, symptoms that have

been measured years following termination of cocaine use (Jaffe, 1985). This extremely long-lasting effect of prolonged cocaine use indicates that significant changes to reward and motivational processing must occur because of cocaine administration. One theory for the route of these neuro-biological changes is via alterations in the shape and structure of nerve cells within the NAc (Robinson & Berridge, 2001). Experimental analysis of cell structures within the NAc prior to and following prolonged cocaine self-administration (1-month duration) indicates that there was a significant increase in dendritic branching and dendritic spine density on medium spiny neurons in the NAc shell (Robinson & Berridge, 2001). These changes in dendrite number and density would alter patterns of synaptic connectivity within limbic pathways, adding to cocaine's motivational, incentivizing, and addictive qualities (Robinson & Berridge, 2001). In normally functioning brains, DA release within the NAc incites emotional states of pleasure and satisfaction, often linked to the individual performing evolutionarily adaptive behavior to incentivize repetition of the beneficial behavior. The presence of cocaine disrupts the effective release and reuptake of DA by NAc cells, creating powerfully pleasurable experiences and incentivizing repetition of cocaine using behavior (Koob, Sanna, & Bloom, 1998).

Social Stress

Escalation of cocaine use from recreational to uncontrollable is frequently initiated during stressful experiences in the individual's life (Rajita Sinha, Catapano, & O'Malley, 1999). Much of the stress experienced by those suffering from cocaine use disorder can be defined as social stress, or stress that stems from relationships with others and interactions with a social environment (Smith & Lazarus, 1990). In humans, environmental and social stress are evaluated through self-report measures and structured interview assessments, but these models are not appropriate for study in animal models, as animals are not capable of responding coherently to verbal questioning. As such, there are a number of methods for examining social stress in animal models, designed to capture various aspects of human social interactions. Many human social interactions are non-hostile, and tests of social interaction,

social choice, and partner preference are used in rodents to mimic these exchanges (Millan & Bales, 2013; Sandi & Haller, 2015). However, even situations that are not overtly threatening could be considered hostile, when social standing, influence, or rejection are at risk.

Commonly used animal models for these kinds of situations are social defeat tests, one example of which is the resident-intruder tests, where the experimental animal is exposed to a dominant resident in its home cage to simulate loss of social ranking, or subordination tests, where animals are continuously housed with an aggressive resident (Buwalda et al., 2011; Koolhaas et al., 2013; Koolhaas et al., 1997; Miczek, 1979). Social rejection or defeat represents a significant stressor in social animals, and an individual's standing in a social hierarchy greatly impacts the health and well-being of that individual (Adler et al., 1994; Sapolsky, 2005). There are many variations of the resident-intruder test used, which may involve different housing conditions prior to and following stress exposure, numbers of exposures to the resident (acute vs. repeated) and have different time courses and criteria for termination of encounter (Palanza, 2001). Historically, the generalizability of social defeat test results was thought to be limited by the lack of observed effects in female intruders, and by the lower levels of aggression in resident females. As such, stress paradigms like social instability tests were more commonly used to mimic the social stress observed in human females (Haller, Fuchs, Halász, & Makara, 1999). However, recently published social defeat stress models where female mice were the intruders indicate that, under specific defeat conditions, females will display stress effects similar in magnitude and symptomology to males (Harris et al., 2017; Schmidt et al., 2010; Takahashi et al., 2017).

In animal models, the effects of brief social stress episodes have been found to be opposite the effects of continuous subordination stress (Miczek, Nikulina, Shimamoto, & Covington, 2011; Covington & Miczek, 2005; Fuchs, Czéh, & Flügge, 2004; Miczek et al., 1999; Sgoifo et al., 2002; Tornatzky & Miczek, 1993). Intermittent stress exposures, when experienced repeatedly, augments

motor-stimulating effects of psychostimulant drugs such as cocaine, and has been shown to reinstate extinguished cocaine-seeking behavior (Miczek et al., 2011). In contrast, prolonged exposure to uncontrollable subordination stress causes dysfunction in reward systems, producing anhedonia-like behaviors (Rygula et al., 2005). Following intermittent social defeat, substantial physiological and behavioral changes are observed in male rodents. In the short term, disruptions in heart rate, body temperature, and hormone secretions are experienced, while long term impacts are seen in social behavior, disease susceptibility, locomotor activity, and drug preferences (Martinez, Calvo-Torrent, & Pico-Alfonso, 1998; Peters et al., 2012; Sgoifo et al., 1999; Tornatzky & Miczek, 1993).

The effects of social defeat stress are notably resistant to habituation, markedly different from the effects of other stressors like restraint stress or foot shock (Sgoifo et al., 2002; Tornatzky & Miczek, 1993). This may be due to more substantial activation of the sympathetic nervous system by social defeat stress than by other stressful stimuli (Sgoifo et al., 1999). There are also significant changes in hippocampal morphology and function observed in male rodents following social defeat stress. Hippocampal volume is reduced, indicating reduced neurogenesis and dendritic remodeling, and decreased ratios of mineralocorticoid to glucocorticoid receptors in the hippocampus (Buwalda et al., 2001; Czeh et al., 2001; Gould et al., 1998; Magariños et al., 1996; Veenema et al., 2003). These neural changes sustain the behavioral changes elicited by social defeat stress, causing marked and prolonged disruptions to quality of life and susceptibility to disease and drug use.

Sensitization of cocaine related behavior is observed following social stress, as indicated by increased locomotor activity upon cocaine challenge (Miczek et al., 1999). Cellularly, sensitization to cocaine can also be observed, as rodents who underwent intermittent episodes of social defeat stress displayed increased extracellular DA levels in the terminal region of the mesolimbic pathway in response to cocaine challenge (Pierce et al., 1996; Vanderschuren & Kalivas, 2000). In vivo, DA neurons display three main patterns of activity, a hyperpolarized inactive state, a slow irregular, single

spike tonic firing, and burst phasic pattern (Grace & Bunney, 1983). The timing of tonic firing is controlled by an intrinsic pacemaker potential, while phasic activity is dependent on afferent input (Grace & Bunney, 1984). Following social defeat stress, the activity of DA neurons in the NAc is changed in two major ways; tonic levels are elevated and phasic responding to cocaine challenge is heightened. Increases in the proportion of phasic responding has been associated with reward-related cues, suggesting the role of DA neurons in reward processing. The increases observed following social defeat stress may indicate that intermittent episodes act as salient events to prompt phasic DA release and enhance the rewarding effects of cocaine self-administration (Cao et al., 2010; Grace, 1991; Grace, 1995; Grace et al., 2007). Experiments using fast-scan cyclic voltammetry show that significant increases in the frequency of transient DA release were observed during interactions with a hostile resident. During an aggressive confrontation significant increases in burst frequency were detected in VTA DA firing patterns without concurrent changes in the number of spikes per burst. Neurons with lower burst rates during non-aggressive conditions did not switch from non-bursting to bursting types, while neurons with higher burst levels showed increases in bursting (Anstrom, Miczek, & Budygin, 2009). This demonstrated that aggressive confrontations were associated with increases in phasic DA transmission in the mesolimbic pathway in defeated rats (Anstrom et al., 2009).

In a subgroup of rodents experiencing a cocaine binge with continuous 24 hour access to cocaine self-administration, animals will take cocaine at regular intervals for around 12 hours, then enter a pattern of "burst and run" taking before ceasing self-administration entirely (Koob & Kreek, 2007; Tornatzky & Miczek, 2000). Animals subjected to social defeat stress display enhanced responding during the second phase of the binge, persisting longer than control animals, and administering 300 to 400 infusions total individually (Covington & Miczek, 2005; Quadros & Miczek, 2009). The results of this experiment suggest that the mechanism for escalated cocaine taking behavior

is mediated by increases of extracellular DA levels within the nucleus accumbens, pointing to a potential mechanism of escalated cocaine taking following stressful experiences.

Materials and Methods

Subjects

Experimental Animals

Male Long-Evans rats (n=9; Charles River Laboratories, Wilmington, MA) weighing 225-250g upon arrival were housed individually in custom-built clear acrylic chambers (30 x 30 x 24.5 cm) lined with cellulose pellet bedding (Cellu-Dri™, Shepherd Specialty Papers, Kalamazoo, MI). Animals were maintained on a reversed light/dark cycle (lights on from 20:00-08:00) inside a climate controlled vivarium. Food and water were provided ad libitum. All animals were permitted to habituate for at least one week prior to initiation of experiments. All procedures were approved by the Tufts University Institutional Animal Care and Use Committee and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council 2011).

Residents as Stimulus Animals

An additional ten male Long-Evans rats were housed in a separate vivarium, pair-housed with female Long-Evans rats. Vivarium conditions were similar to experimental animals. The residents were housed in large stainless-steel chambers (45.7 x 71.1 x 45.7 cm) lined with sawdust bedding. Residents served as aggressive stimulus animals for the social defeat protocol and were screened regularly for aggressive behavior with naïve male "intruders".

Social Defeat Stress in Intruders

Experimental animals were exposed to episodic social defeat as previously described (Boyson et al., 2014; Covington & Miczek, 2001; Tornatzky & Miczek, 1993). Social defeat exposures happened on experimental days 1, 4, 7, and 10. Animals were placed for 10 minutes in a protective wire mesh

cage, positioned within the resident's home cage. Following this instigation phase, intruders were removed from the protective cage and reintroduced to the resident's home cage, where an aggressive encounter ensued. Encounters were terminated after 6 seconds of the intruder displaying a submissive "supine" posture, 10 bites by the resident, or 5 minutes following the first attack bite, whichever came first. Immediately following the fight, intruders were returned to the protective cage and placed within the home cage for an addition 10-minute period of social threat. All social defeat encounters were observed, and the attack latency, total attack bites, fight duration, and time supine were recorded by the experimenter.

Cocaine Self Administration Training

Intravenous Catheter Surgery

One day following the final social defeat exposure, rats were anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (6 mg/kg, i.p.) and implanted with an indwelling catheter (Silastic® silicon tubing, ID 0.63 mm, OD 1.17 mm) into the right jugular vein, under sterile surgical procedures. Catheter tubing was threaded subcutaneously from the jugular entry site to the animal's back, where it exited through a small incision between the scapulae. Outside of the skin, tubing was affixed to a plastic pedestal mounted within an adjustable harness (SAI Infusion Technologies). Rats were permitted to recover for 5 days in their home cage (as described above) prior to initiation of self-administration training. Upon recovery, rats were housed in intravenous self-administration chambers with the same dimensions and bedding conditions as the home cage, for the remainder of the experiment. Overnight, saline was delivered in 0.17 mL pulses every 30 minutes to maintain patency of catheters. Every morning, catheters were flushed with 0.20 mL saline and 0.20 mL of heparinized saline (20 IU/mL), also to maintain catheter patency.

Cocaine Self Administration Training

Acquisition and Maintenance

Self-administration sessions were conducted within the modified home cage, which had a removable panel containing two retractable levers and two stimulus lights (Med Associates Inc.). Chambers were positioned within sound and light attenuating enclosures, equipped with ventilation fan and house light. During acquisition of self-administration, each response on the active lever (Fixed Ratio: FR1) was reinforced with 0.75 mg/kg cocaine infusion, which occurred simultaneously with illumination of a green stimulus light, and followed by a 30 second post infusion timeout period. Responding on the inactive lever and responses during the timeout were recorded but did not result in a consequence. All sessions were terminated after 15 infusions or 5 hours, whichever happened first. Criteria for acquisition of training were defined as 15 infusions obtained on 2 continuous days. Differences in acquisition rates across treatment conditions were not evaluated due to interventions made to ensure that all animals acquired. Following acquisition, the response requirement was increased stepwise until every fifth response results in cocaine infusion (FI5) over the course of 2 to 3 days. Self-administration performance was then maintained on an FR5 schedule of reinforcement for a minimum of 10 sessions prior to testing on the 24-hour extended access binge.

Intracranial Surgery

After 3-5 sessions of stable cocaine self-administration on FR5, rats were anesthetized with ketamine (100 mg/kg) and xylazine (6 mg/kg) and surgically implanted with unilateral guide cannula (Synaptech) aimed at the NAcSh using coordinates from a stereotaxic atlas (anteroposterior: +1.6 mm

from bregma; mediolateral: +1.1 mm from bregma; dorsoventral: -5.8 mm from dura). Rats were allowed to recover for at least 5 days before resuming self-administration.

In vivo **Microdialysis**

24 Hour Binge

Starting 2 hours into the dark phase (10:00), rats were given unlimited access to cocaine (FR5, 0.3 mg/kg/infusion) for 24 hours. The total number of infusions was recorded as the primary dependent measure between groups. Immediately following completion of the binge (at 10:00 the next day) catheter patency was evaluated by administering 0.20 mL Propofol (10 mg/kg). Upon completion of the experiment, rats were perfused, and brains were extracted to confirm cannula placement. Perfused brains were sliced to a thickness of 30μm and stained with cresyl violet to determine the termination point of the probe cannula.

DA Sample Collection

Animals were allowed to recover for 5 days following intracranial surgery during which FR5 cocaine self-administration was continued to recover pre-surgery performance prior to the binge. At least two sessions were conducted with the microdialysis head-mount and fluid swivel (SAI) attached to allow the animal to habituate to the apparatus prior to binge testing.

The day before sample collection, the fluid swivel (SAI) was replaced with an Instech 2 channel swivel (375/D/22QE) which contained 1 quartz-lined channel for microdialysis, and 1 22G stainless steel channel for cocaine/fluid delivery. Additionally, the rats were briefly anesthetized with isoflurane and the microdialysis cannula stylet was replaced with a 2mm active membrane probe (Synaptech) connected to a syringe filled with aCSF (CMA Microdialysis). The infusion rate was set to 0.5 μL/min overnight and was increased to 1.5 μL/min 1 hours before sample collection the next day.

During the binge protocol, cocaine was delivered through the stainless-steel channel and aCSF for sample collection was delivered through the QL channel. The output line was secured outside the

cage, and samples were collected manually. Samples were collected every 20 minutes into vials containing 5 μL antioxidant solution (0.2M Acetic acid containing 6.0mM L-Cysteine and 2.0mM Oxalic acid, pH 3.2). Tonic levels of DA were assessed in 5 baseline samples, followed by samples taken every 20 minutes during the 24-hour binge.

In vivo **Microdialysis**

Post Binge Cocaine Challenge

Immediately following termination of the 24-hour binge, cocaine self-administration was stopped and an additional 5 samples (20 minutes apart) were collected to reestablish baseline DA concentrations. After 5 baseline samples, 1.0 mg/kg cocaine was infused intravenously, and samples were collected for an additional 120 minutes (6 samples).

HPLC Analysis

DA concentrations were analyzed using high-performance liquid chromatography, which consisted of an HTEC-510 system (EICOM) and manual injector (model 9725i, Rheodyne) with a 100 μL sample loop. Mobile phase composition was 0.1M phosphate buffer, 0.134mM 2Na-EDTA, 2.29mM DSS, and 15% methanol, with pH adjusted to 5.4 and flow rate set to 0.5 ml/min. A reversed phase separation column (FA-3ODS, EICOMPAK, 3.0mm φ x 75mm, EICOM) with temperature set to 25°C was used to separate monoamines, which were then analyzed using an electrochemical detection system (HTEC-510, EICOM) with a graphite working electrode (WE-3G, EICOM). DA concentrations were calculated using a standard curve with known amounts of monoamines in a range of 0.5 – 5.0 pg and detection limit for DA was approximately 0.18 pg.

Corticosterone Analysis

Blood Collection

Blood samples were collected one week prior to starting cocaine self-administration training to establish individual baseline levels, and during the 24-hour binge protocol. Samples were collected by drawing from the catheter port at 5 regular time points during the day/night cycle (09:00, 14:00, 21:00, 02:00, 09:00 next day). A 1 mL syringe was used to draw 0.3 mL of blood, which was replaced by 0.3 mL of heparinized saline (20 IU/mL) pushed through the catheter port.

Sample Preparation

Samples were centrifuged for 7 minutes at 4º C at 3,500 revolutions per minute, after which 60 μL of blood plasma was collected.

Corticosterone Assay

A corticosterone enzyme immunoassay kit (Arbor Assays, Ann Arbor, Michigan) was used to analyze the samples for corticosterone. Detection levels for corticosterone were 7.8125 ng/mL.

Results

Probe Placements

All probes were determined to terminate in the shell of the NAc (Fig.1 right). Fig. 1 (left) shows a representative image of tissue sliced to 30 μm and stained with cresyl violet.

Acquisition and Maintenance

All animals reached acquisition criteria (minimum 0.5 responses/min, 0.3mg/kg cocaine per infusion, for 5 consecutive sessions) by the ninth self-administration session. Control animals maintained a stable rate of responding (0.801 ± 0.130 responses/min) from session 5 to session 10. The defeat-experienced animal continued to increase response rates from session 5 to session 10, reaching a maximum response rate of 2.22 responses/min during session 9 (Fig. 2).

Corticosterone

Baseline

Control animals without defeat experience displayed baseline diurnal corticosterone levels which were cyclical and were similar to previously reported data. Corticosterone levels were highest within the first few hours of the dark phase (9am, ZT13) and were lowest within the first few hours of the light phase (9pm, ZT1) (Fig. 3).

Binge

The diurnal corticosterone levels displayed by control animals during 24-hour cocaine binging were comparable to baseline levels. Concentrations and rhythmicity were unchanged (Fig. 4).

24-Hour Binge

Self-Administration Behavior

Total cumulative responding was higher in the defeat-experienced animal (n=1) than in control animals (n=8). The defeat-experienced animal responded 478 times (143.4 mg/kg cocaine), while control animals responded 271.83 ± 40.60 responses (81.55 ± 12.18 mg/kg cocaine) (Fig. 5). During the first three hours of the binge (0 min to 180 min), control animals responded 24.06 ± 4.604 times (7.22 ± 1.38 mg/kg cocaine), while the defeat-experienced animal responded 97 times (29.1 mg/kg cocaine) (Fig. 6A). During a three-hour period near the end of the binge (700 min to 880 min), the defeat-experienced animal responded 83 times (24.9 mg/kg cocaine) while control animals responded 37.17 ± 9.79 times (11.15 ± 2.94 mg/kg cocaine) (Fig. 6B).

Dopamine Concentrations, 24-hour Binge

Recovery of microdialysis probes was determined *in vitro* at the end of the experiment. After removal from the rat brain at the end of the binge, probes were immersed in a vial containing 10 pg DA and were perfused with aCSF at a rate of 2 μL/min. After at least 30 minutes, a 20-minute sample was collected into a 0.5 mL Eppendorf Protein LoBind tube, and the sample was run through the HPLC. Mean probe recovery was 14.21%.

Prior to initiation of the cocaine binge, baseline DA concentrations were determined to be 2.77 ± 0.24 pg/μL in control animals and 1.84 ± 0.11 pg/μL in the defeat-experienced animal (Fig. 7A). During the first three hours of cocaine binge, DA concentrations were determined to be 8.94 ± 1.61 pg/μL (302.75 ± 54.67 % of baseline) in control animals and in the defeat-experienced animal the DA concentration was 8.23 ± 0.35 pg/μL (453.98 ± 19.12 % of baseline) (Fig. 7B). During a three-hour period near the end of the binge (700 min to 880 min), the defeat-experienced animal had a DA concentration of 9.72 ± 0.88 pg/μL (535.55 ± 48.62 % of baseline) while control animals had DA concentrations of 3.22 ± 1.27 pg/μL (108.53 ± 35.23 % of baseline) (Fig. 7C).

In both defeat-experienced and control animals, administration of cocaine increased dialysate DA levels from baseline concentrations. As shown in the individual records in Figs. 8 & 9, changes in response rate for cocaine corresponded well to the observed fluctuations in DA levels across stress conditions. The amounts of DA elicited by cocaine self-administration was higher in the defeat-experienced animal than in control animals. At the end of the 24-hour duration, the defeat-experienced animal established a new, higher baseline (0.500 pg/μL), which was maintained for at least 3 hours (Fig. 9).

DA Undershoot

In all animals that terminated self-administration of cocaine, a prolonged undershoot of DA concentration below established baselines was observed (Fig. 9). There was not a substantial apparent difference in magnitude of the undershoot, as control animals showed an undershoot of 76.36 ± 10.81% from baseline, while the defeat-experienced animal showed an undershoot of 82.18 ± 7.06 % from baseline. Control animals did not recover baseline DA concentrations within a 240-minute time period, while the defeat-experienced animal recovered baseline DA concentrations after 180 minutes (Fig. 10). The results from control animals are supported by previous experiments involving non-stressed rats bingeing cocaine, which indicated that DA concentrations did not recover to baseline levels during a 6 hour time period following termination of the binge (Parsons et al., 1995).

Post-binge Cocaine Challenge

Following the 24-hour binge, new baseline DA concentrations were established for 80 minutes. Animals were then injected with 1.0 mg/kg IV cocaine, and DA concentrations were measured for the following 120 minutes (Fig. 11A). Administration of the challenge dose of cocaine did not elicit an increase in DA in control animals (0.42 ± 0.081 pg/μL, 119.45 ± 15.92 % baseline, Fig. 11B), but did elicit a substantial increase in DA concentrations in the defeat-experienced animal (1.50 pg/μL, 299.52 % baseline, Fig. 11C).

Discussion

The current experiments examine potential differences in DA neurotransmission in the NAc shell during a prolonged cocaine binge, in rats previously exposed to social defeat stress. Socially defeated animals display prolonged and escalated cocaine intake, which may be due to alterations in DA neurotransmission (Covington & Miczek, 2001, 2005; Pierce et al., 1996; Vanderschuren & Kalivas, 2000). These changes could represent an underlying DA mechanism that contributes to addiction and substance abuse disorders.

One notable difference observed is that the defeat experienced animal displayed lower baseline concentrations of DA than non-defeated controls, yet achieved similar levels of DA during active cocaine binging, representing a larger *relative* change in extracellular DA from baseline. Behaviorally, these animals self-administered cocaine at a higher rate, and for a longer duration than controls, which parallels previous reports on stress-escalated cocaine binges (Covington & Miczek, 2001, 2005; Leonard, DeBold, & Miczek, 2017). Upon termination of self-administration, all rats displayed a prolonged reduction in DA concentration below previously established baselines. Although this undershoot was similar in magnitude between defeat-experienced and non-defeated controls, defeat-experienced animals were quicker to recover basal extracellular DA levels. The deficits observed in non-defeated controls were accompanied by a profound neurochemical insensitivity to cocaine challenge, where acute cocaine infusion failed to elicit a change in accumbens DA content, while no functional deficit was observed in defeat-experienced animals. It is possible that animals who have experienced intermittent social defeat stress may be less susceptible to cocaine-induced DA terminal dysfunction, which could contribute to the prolonged bouts of self-administration characteristic of this population (Mateo et al., 2005).

A distinct DA deficiency has been observed in rats with many types of drug dependency, including alcohol and morphine (Diana et al., 1999; Rossetti et al., 1991). These historical findings

indicate that, for drug of abuse, DA hypofunction develops slowly and persists even after secession of withdrawal symptoms (Dackis & Gold, 1985; Koob et al., 1989). The prolonged decrease in basal DA activity is hypothesized to promote craving and/or drug seeking to restore pre-drug neurotransmitter levels (Dackis & Gold, 1985; Koob et al., 1989). Notably, we found that a defeat-experienced animal displayed a lower DA tone than non-defeated controls, although this has not been shown in other published work (Boyson et al., 2014; Holly et al., 2012). Additionally, the defeat-experienced animal self-administered cocaine at an increased rate compared to control animals while achieving equivalent extracellular DA concentrations. Together, these findings align with the DA deficiency hypothesis, as self-administration behavior may be aimed to recover from the DA deficient state by eliciting higher levels through the action of cocaine at DA terminals (Diana, 2011). Indeed, it has been shown that drug seeking behavior is enhanced when in a state of low DA tone, which may factor into the high rates of self-administration displayed in the defeat-experienced animal (Twining et al., 2015).

Following termination of cocaine self-administration, accumbens DA concentrations in the defeat-experienced animal stabilized at a significantly higher level than the pre-binge measurements, which was comparable to control values. This observation is inconsistent with expected concentrations based on the DA deficiency hypothesis. As the defeat-experienced rat had initially low baselines and administered cocaine for a longer duration, it was anticipated that post-binge concentrations would be additionally lowered, which was not observed. The increased DA concentration in the defeat-experienced rat may indicate that the experience of social defeat stress is sufficient to disrupt typical responses to prolonged cocaine exposure.

It is important to note that, although the DA concentrations elicited by cocaine self-administration were comparable between defeat-experienced and control animals, the *relative* changes

were not. It has been shown that the phasic response to reward is correlated to the magnitude of that reward, suggesting a greater relative neurochemical response to rewarding stimuli of greater value (Gan, Walton, & Phillips, 2010; Schultz, Dayan, & Montague, 1997). Although the defeat-experienced rat showed peak DA concentrations equivalent to controls, it experienced a greater relative increase from baseline, which may indicate that it experienced greater rewarding effects of cocaine self-administration, therefore altering response patterns.

Additionally, defeat-experienced animals have shown greater relative responses in locomotor activity and DA concentrations to non-contingent cocaine administered during cocaine challenges, which was also shown in this experiment (Boyson et al., 2014; Covington & Miczek, 2001). This may suggest that exposure to social defeat stress produces sensitization to cocaine's neurological effects, facilitating the release of DA following cocaine binge (Covington & Miczek, 2001). Sensitization may also impact cocaine intake, increasing intake in defeated animals, as observed in this experiment. This could potentially facilitate the transition from recreational to compulsive drug seeking and taking behavior (Covington & Miczek, 2001).

Data from the last six hours of this experiment replicated findings published by Parsons, Koob, and Weiss (1995), where dialysate DA concentrations decreased below baseline following termination of cocaine self-administration, and remained lowered for an extended duration. It is theorized that rats begin to experience withdrawal symptoms almost immediately after cessation of cocaine taking, which can last for up to 72 hours (Markou & Koob, 1991). Previous research suggests that there is a positive correlation between duration of self-administration session and degree of DA suppression and deficits in stimulation during withdrawal (Markou & Koob, 1991; Weiss et al., 1992). While these findings were replicated in the non-defeated control rats, this was not true of the defeat-experienced animal. This rat displayed the longest self-administration duration, without a

corresponding increase in DA levels. In addition, only the defeat-experienced animal recovered basal DA concentrations within four hours of termination of self-administration. Although a more robust sample is required to examine this preliminary finding, it is possible that the defeat-experienced animal experienced a restoration of DA function, while the non-defeated controls experienced the loss of function displayed in previous studies. Elevated levels of DA maintained during extended cocaine self-administration may result in a general decrease in DA signaling, producing a hypodopaminergic state (Dackis & Gold, 1985; Koob et al., 1989). This decrease may be due to a variety of factors, including changes to presynaptic DA autoreceptor density (Gao et al., 1998; Marinelli et al., 2003; Zhang et al., 1997), increased DA uptake through alterations to DAT functioning or other uptake mechanisms (Yolanda Mateo et al., 2005; Wheeler et al., 2017), and/or augmented enzymatic degradation (Mercuri et al., 1997). Additionally, changes to DAT functioning have been observed following exposure to social defeat stress, which may produce elevations in cocaine self-administration behavior (Brodnik et al., 2017). The down-regulation is thought to cause a decline in DA concentrations following the emergence of withdrawal symptoms, establishing low DA tone to which drives further drug seeking behavior (Diana et al., 1999; Parsons et al., 1995). The results from this study suggest that defeat-experienced animals may be more resilient to cocaine induced changes to DA terminal function, allowing the DA concentrations to more quickly return to pre-session baselines.

These differences in DA terminal function are most strikingly demonstrated by the neurochemical response to non-contingent cocaine administration after a 24-hour binge. Non-defeated control animals did not show an elevation of extracellular DA following administration of 1.0 mg/kg IV cocaine. These findings replicate previous work by Mateo et al. (2005), which demonstrated a lack of DA elicited by cocaine following 10 days of binge-like cocaine self-administration, suggestive of a hypodopaminergic state established by increased clearance of extracellular DA through alterations in DAT functioning. In contrast, non-contingent cocaine elicited

a large extracellular DA increase in the defeat-experienced rat, similar to the patterns of cocaine-naïve animals (Yolanda Mateo et al., 2005). These findings suggest that in cocaine-experienced, non-defeated animals, there is a marked decrease DA neurotransmission due to cocaine, as in the DA depletion hypothesis (Dackis & Gold, 1985; Yolanda Mateo et al., 2005).

At this time, it is not possible to conclusively separate the circadian effects of mesolimbic DA functioning from the effects of accumulated cocaine, obscuring mechanistic determination. The non-defeated control rats in this study displayed cocaine binges with the characteristic circadian pattern previously seen, where self-administration decreases during the second half of the light-cycle, regardless of when the rat began self-administration (Baird & Gauvin, 2000; Roberts et al., 2002). As observed in this study, peak responding for psychostimulant administration is displayed during the dark phase of the light cycle (Terman & Terman, 1970; 1975), while responding terminates around ZT11 or the transition between light and dark. This transitional time point has also been associated with reduced conditioned place preference induced by psychostimulants, suggesting that the effects of psychostimulants may vary across the light cycle (Baltazar, Coolen, & Webb, 2014; Webb et al., 2009). It was found that acquisition of cocaine self-administration was slower during the light phase, potentially due to decreased effects of cocaine on DA neurotransmission (Ozburn et al., 2012). Therefore, cocaine self-administered during the light phase may simply fail to elicit the same magnitude of DA increase as in the dark phase, and individuals may be more likely to terminate responding. Indeed, we found that a non-defeated control animal (#603) which began its binge self-administration during the last three hours of the light phase, failed to show typically augmented extracellular DA concentrations during initial cocaine self-administration, and terminated drug-taking after only 2 hours. However, as the session progressed into the dark-phase, this animal resumed drug-taking, which then produced a 3-fold increase in accumbens DA. Diminished cocaine-elicited DA was also apparent during the light phase in the non-stressed rats, although this observation cannot be

attributed to circadian factors alone, as accumulated cocaine likely influenced DA terminal function as well, as previously discussed.

Within this experiment, the defeat-experienced animal did not show a decreased response to cocaine during the light phase, and in fact maintained peak DA concentrations during this period. It has previously been shown that defeat-experienced rats do not show circadian patterns of cocaine self-administration, regardless of the onset of drug access (Covington et al., 2005; Fowler et al., 2007). The observed lack of circadian rhythmicity in self-administration and extracellular DA could be due to a disruption in the diurnal factors regulating DA neurotransmission following stress exposure. Changes in DA reuptake via DAT are thought to mirror tonal fluctuations, which are removed when DAT functioning is decreased. Diurnal changes in DA concentration are dependent on DAT functionality, suggesting that DAT may be a mechanism for stress mediated changes in DA reuptake. Stress has been shown to alter functioning of DAT in cocaine self-administering rats, and DAT expression is highly implicated in regulation of DA rhythmicity, therefore changes in receptor trafficking may be implicated in the observed changes in DA tone (Brodnik et al., 2017; Ferris et al., 2012). However, as qPCR of NAc DAT mRNA did not show a general downregulation in the defeat-experienced animals, additional examinations of DAT surface expression and conformational changes are necessary to support or refute this potential mechanism.

DAT is an important potential target for study, as the psychomotor stimulant effects of cocaine are thought to be due to inhibition of DAT functioning, leading to decreased DA reuptake. Cocaine and its analogues are true competitive inhibitors of DAT, binding between transmembrane domains 1, 3, 6, and 8, which overlaps considerably with the DA binding site (Beuming et al., 2008). When cocaine is bound to DAT, it physically blocks DA from entering its binding site, preventing reuptake into the presynaptic neuron, therefore it was previously theorized that removal of DAT

would prevent self-administration behavior. A study examining cocaine self-administration in DAT knockout mice found an unexpected maintenance of cocaine-self administration behavior, indicating a shift in cocaine's mechanism of action (Rocha et al., 1998). Essential DA systems are disrupted by a lack of DAT, indicating a necessity for alternate mechanisms of DA reuptake which is not observed in wild-type animals. Structural similarities between DAT and the serotonin transporter protein (SERT) suggest that cocaine will bind to SERT in the absence of DAT, and cocaine binding to SERT was shown in DAT-KO mice (Rocha et al., 1998; Beuming et al., 2008). Additionally, the norepinephrine transporter protein (NET) has a similar structure to DAT and SERT, suggesting it may be another site of cocaine action in DAT-KO mice. However, inhibition of both NET and SERT fails to elicit a change in DA clearance or evoked release in the NAc in DAT-KO mice, suggesting that cocaine acts primarily outside the NAc, potentially through elevated serotonin levels in the VTA (Budygin et al., 2002; Mateo et al., 2004). In wild-type mice, the relative affinities for DA are significantly higher for DAT than for SERT or NET, suggesting that even when DAT functioning is inhibited by cocaine, DA reuptake will not be shifted to other transporter proteins, further emphasizing the role of DAT functioning in cocaine taking and seeking behaviors.

A clear connection has been shown between stress exposure and drug abuse. In both animal and human models, reciprocity between stress and drug abuse is observed (Beardsley, 2005; Sinha, 2001) It is thought that stress may act as a potentiator, initiating state-dependent changes in brain reward circuitry, heightening sensitivity to the reinforcing properties of drugs and enhancing the potency of drugs of abuse or drug-associated cues to induce relapse. Along with direct engagement of motivational circuitry, exposure to stressful stimuli leads to activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, causing release of glucocorticoid hormones, cortisol in humans and corticosterone in rodents, which have a nuanced relationship with drug-relapse. Elevated cortisol and heightened HPA reactivity are associated with enhanced drug craving and relapse susceptibility in

human users (Berger et al., 1998; Sinha et al., 2003; 2006), while in rodents, heightened glucocorticoid levels can enhance behavioral and neurochemical responses to drugs of abuse (Piazza et al., 1996; Marinelli et al., 1997). Literature suggests that glucocorticoids alone may not drive drug seeking or relapse, but that they do interact with drugs and drug-associated stimuli to promote the likelihood of drug use. In rats, acute stress has been shown to potentiate the effects of cocaine on drug-seeking behavior, with corticosterone as a necessary mediator of the interaction. Corticosterone decreases DA clearance within the NAc, a critical site for the potentiating effects of cocaine, and corticosterone-induced inhibition of DA reuptake enhances sensitivity to changes in DA neurotransmission and behavior elicited by cocaine. This may indicate corticosterone as a key mechanism by which stress modulates DA neurotransmission, resulting in alterations in drug seeking behavior (Graf et al., 2013; Wheeler et al., 2017).

Corticosterone may also regulate diurnal DA functioning, through its distinct diurnal pattern of release (Malisch et al., 2008). In rodents exposed to stress, rhythmic secretion of corticosterone is significantly and persistently altered, producing a blunted and phase shifted corticosterone rhythm (Aslani et al., 2014). In non-defeated rats, there was no difference observed in corticosterone levels between pre-cocaine baseline and during cocaine binging, with both following established diurnal patterns (Butte, Kakihana, & Noble, 1976). It has been demonstrated that defeated animals display increased levels of corticosterone following social defeat, which may influence the activity of DA neurons, therefore compounding the escalatory effects of cocaine intake (Marinelli & Piazza, 2002; Piazza & Le Moal, 1998; Piazza et al., 1996; Rodríguez-Arias et al., 2009). Dysregulated corticosterone rhythmicity induced by stress are thought to facilitate the reinforcing effects of cocaine and increase cocaine self-administration, so it is anticipated that defeat-experienced animals would display a dysregulation of corticosterone levels (Ambroggi et al., 2009; Deroche et al., 1997; Piazza et al., 1996). Additionally, dysregulation of corticosterone during binging in defeat-experienced animals may

provide an explanation for the disruption in circadian rhythmicity of self-administration and DA concentrations. Corticosterone levels should be determined in defeat-experienced animals for baseline and binging conditions to contribute to the literature regarding potential sources of diurnal rhythms of drug taking and DA efflux.

One limitation of the microdialysis procedure used in this experiment is the duration of the sampling period. Microdialysis samples were collected over the course of 20 minutes, representing an average of DA concentrations across that time. In this way, acute determination of DA concentrations is not possible. However, as this study was examining self-administration behavior over a 24-hour duration, the selected 20-minute sampling period was determined to be appropriate. Another limitation of microdialysis stems from the potential for cellular damage and neurotransmitter depletion at the sampling site. While the perfusion of aCSF into the region limits tissue damage due to fluid loss, long term sampling may still produce artificial deficits in DA concentrations. To limit the potential for damage, the flow rate during the sampling period was kept low (1 μL/min). If tissue damage occurred following probe implantation, self-administration behavior following surgery would be altered, which was not observed in this experiment. Similarly, if DA concentrations were depleted by sampling, either earlier termination of self-administration or greater intake to elicit DA efflux would likely be observed, therefore overcoming the artificial deficit. Constant perfusion of fluid may cause inflammatory response or gliosis to the region, which may lead to reduced recovery. If probe recovery is impacted, reduced DA concentration at the end of the session could be due to lack of permeability, rather than an actual decrease in extracellular concentrations. In vitro probe recovery determined that there was negligible loss of probe functioning following extended perfusion, indicating that this was not the cause of the observed decrease in concentrations.

This study highlights many potential areas for future analysis. Firstly, additional data following these protocols should be collected to determine if the changes observed between defeat-experienced and non-defeated animals are statistically significant. As discussed earlier, corticosterone levels should be determined in defeat-experienced animals to interrogate corticosterone as a mechanism for the DA fluctuations. Comparisons of diurnal DA rhythmicity between non-binging defeat-experienced and non-defeated controls should be made to determine if baseline DA concentrations are similar, which would provide insight into the mechanism of action of cocaine on DA in defeated animals. Use of no-net flux microdialysis during periods of relatively stable DA concentrations, such as baseline and the observed undershoot following self-administration termination can provide more accurate comparisons of DA concentrations between control and defeat-experienced rats, and analyses during the undershoot can help to characterize and evaluate reuptake of DA. Combined with the present data, these analyses would provide important information regarding mechanistic risk factors in cocaine addiction.

Figures

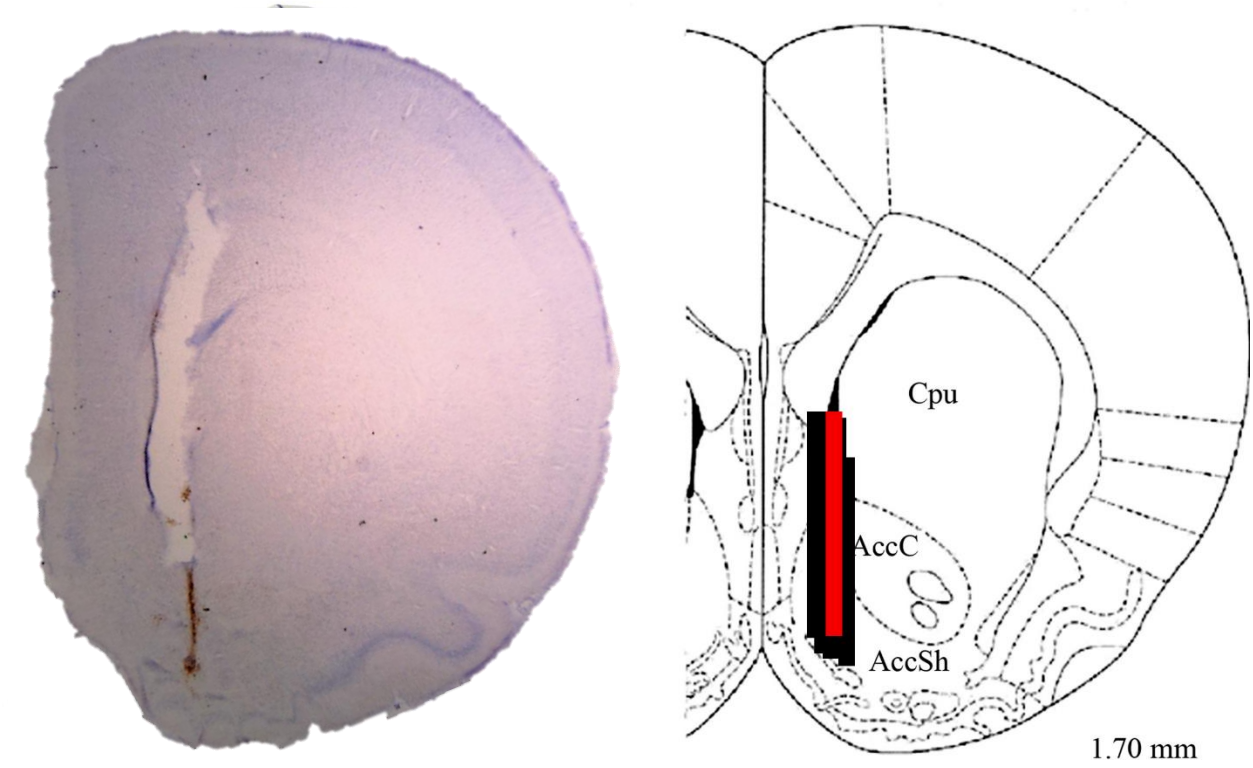

Figure 1.

Histology. A representative photopictomicrograph of probe placement in the NAc Shell is shown on the left, with a schematic on the right depicting all probe placements of control (black) and defeat-experienced (red).

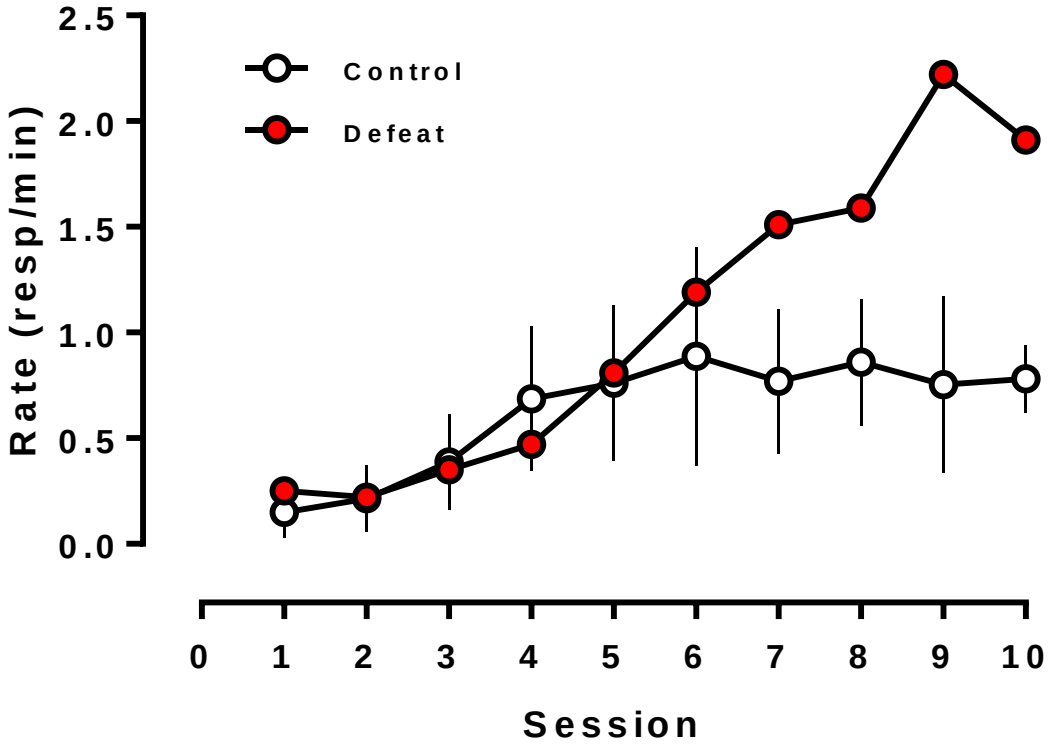

Figure 2.

Acquisition rates for control (red, n=6) and defeat-experienced (white, n=1) animals. Control animals reached stable response rates (0.827 ± 0.356 responses/min) starting with session 4. The defeat-experienced animal never achieved stable response rates, and increased responding from session 4 to session 9. Acquisition criteria were set at a minimum of 0.5 responses/min for 5 consecutive sessions.

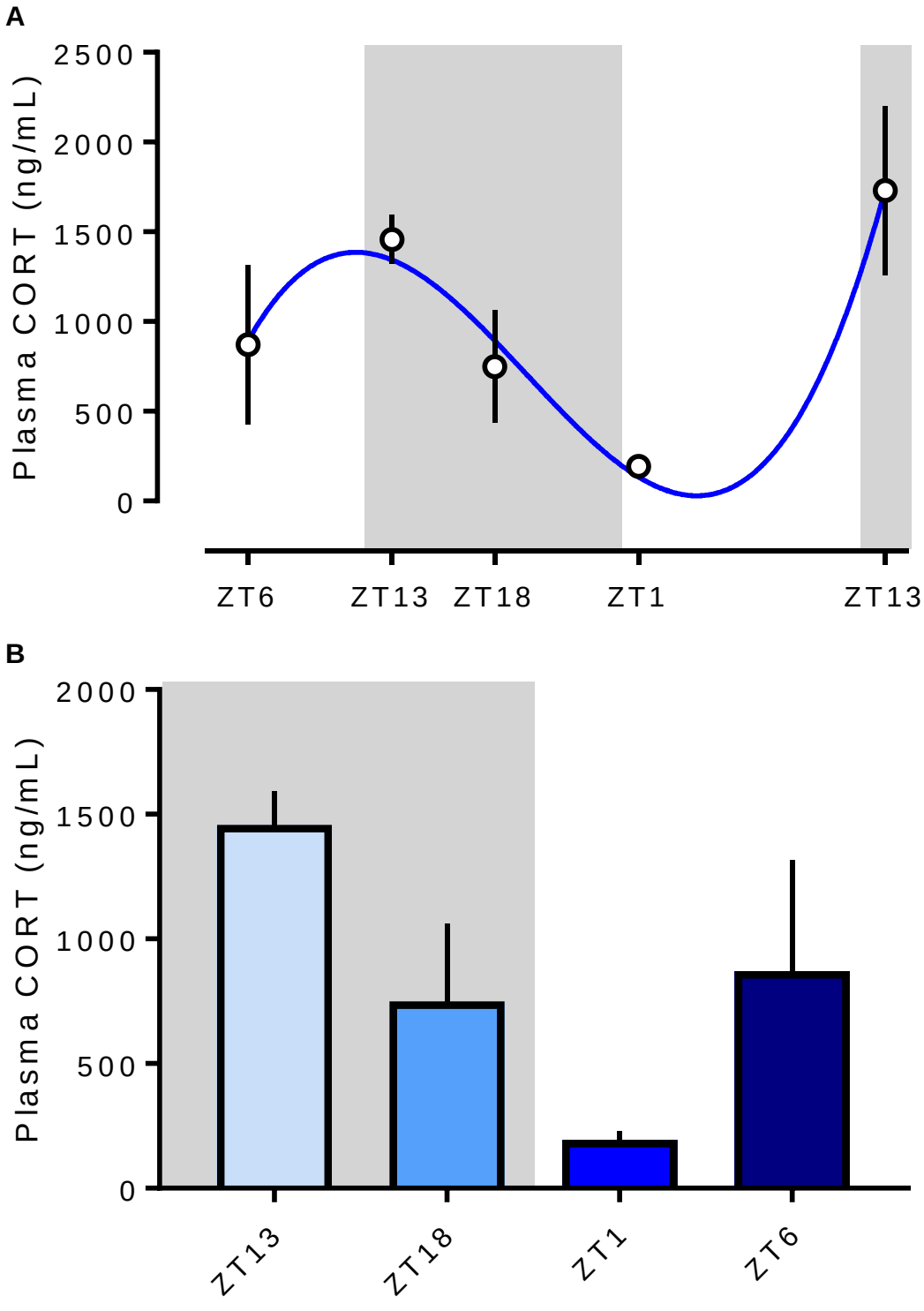

Figure 3.

Corticosterone concentration measurements prior to cocaine experience (baseline), non-defeated controls only (n=4). Levels were highest at ZT13 (9am), and lowest at ZT1 (9pm).

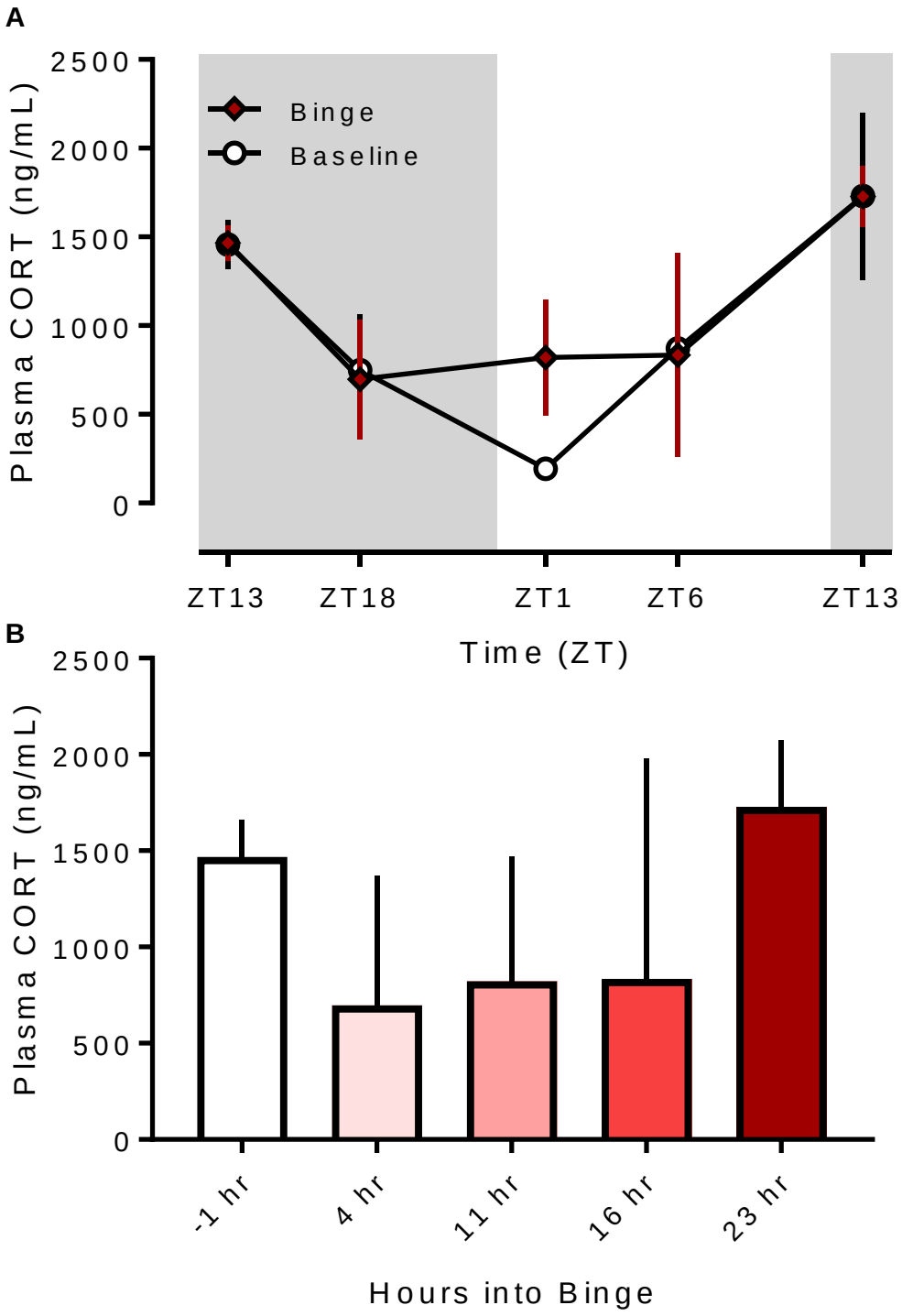

Figure 4.

Corticosterone concentration measurements during 24-hour cocaine binge, non-defeated controls only (n=4). ***A***, Corticosterone levels and rhythmicity were unchanged between baseline and binge conditions. ***B***, Levels were highest at ZT13 (9am), and lowest at ZT1 (9pm).

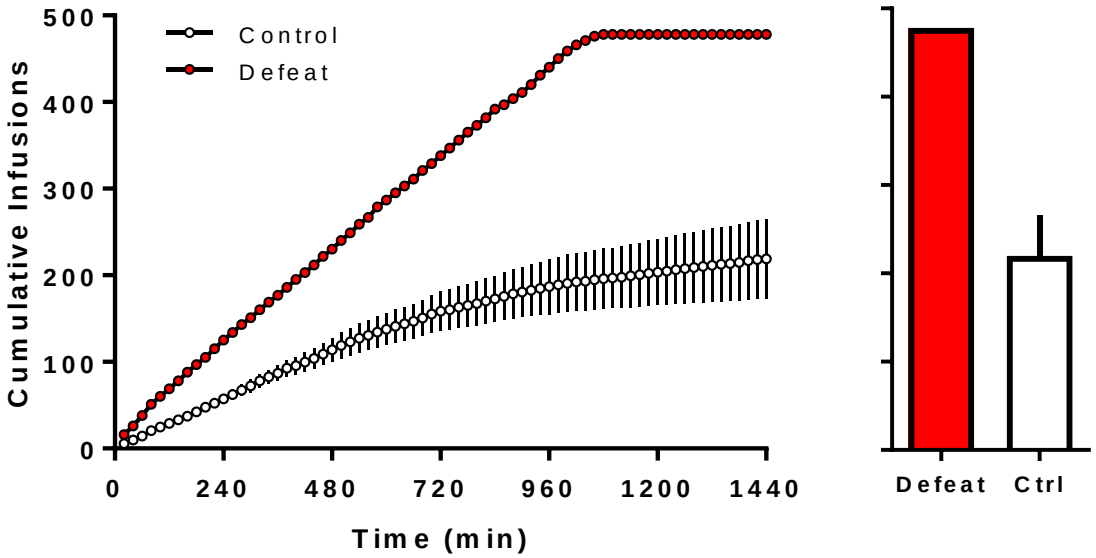

Figure 5.

Impact of social defeat stress on later binge cocaine self-administration. The defeat-experienced rat (red, n=1) self-administered more cocaine during the 24-hour binge compared with non-defeat-experienced controls (white, n=6). Cumulative infusions in 2-hour bins are shown on the left, with total infusions shown on the right.

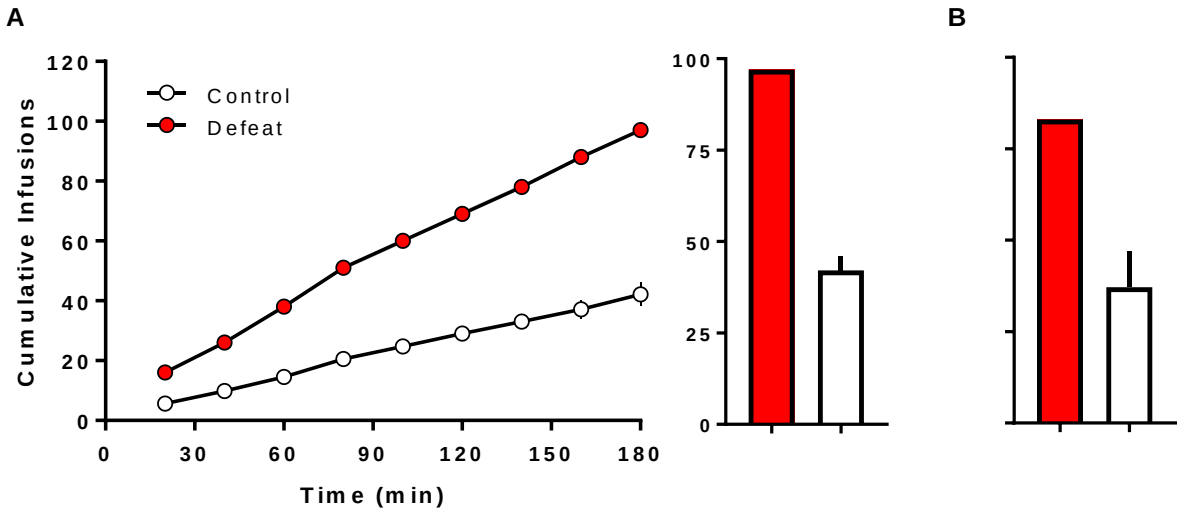

Figure 6.

Impact of social defeat stress on later binge cocaine self-administration, selected time points. ***A***, The defeat-experienced rat (red, n=1) self-administered more cocaine during the first 3 hours of the binge compared with non-defeat-experienced controls (white, n=7). Cumulative infusions in 20 min bins are shown on the left, with total infusions shown on the right. ***B***, The defeat-experienced (red, n=1) rat self-administered more cocaine from 700 minutes to 880 minutes, compared with non-defeat-experienced controls (white, n=6).

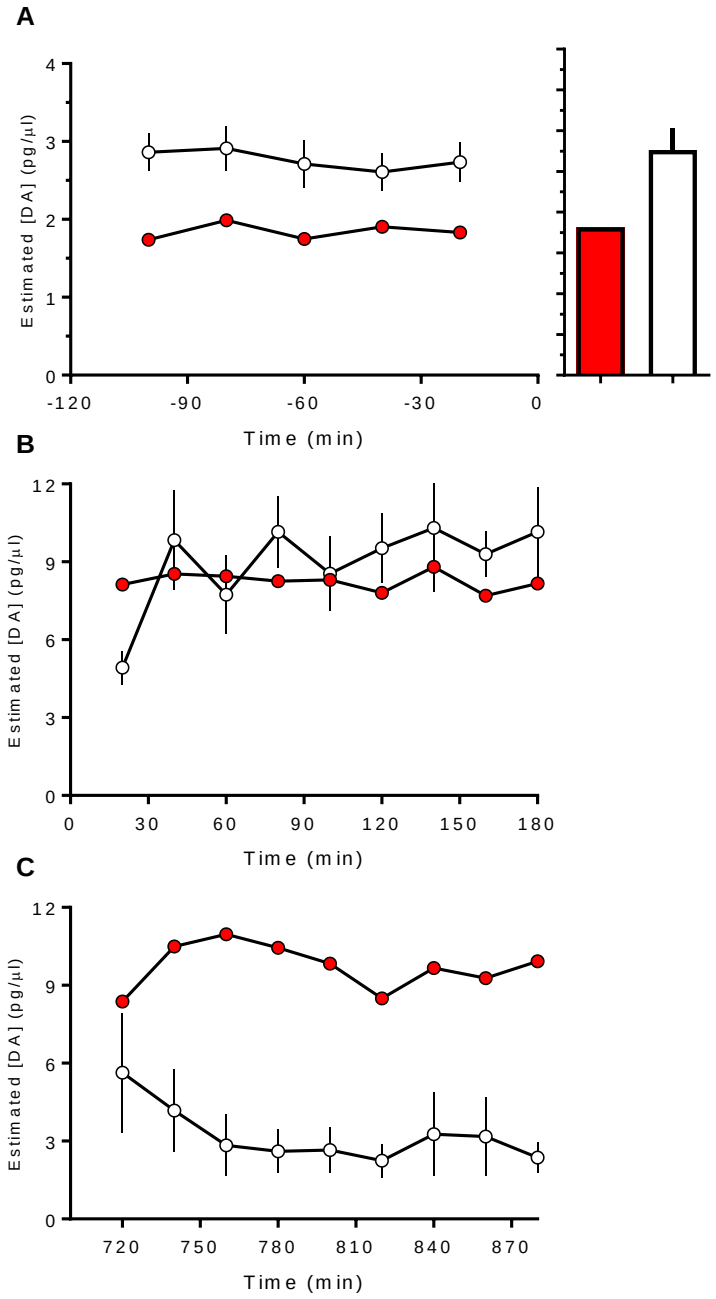

Figure 7.

Impact of social defeat stress on DA concentrations elicited during 24-hour binge. ***A***, The defeat-experienced rat (red, n=1) displayed a lower baseline DA concentration compared to non-defeat-experienced controls (white, n=3). Left, DA concentrations plotted against time in 20-minute bins. Right, average DA concentrations (in pg/µL). ***B***, During the first 3 hours of the binge, the defeat-experienced rat (red, n=1) displayed a lower average DA concentration compared to non-defeat-experienced controls (white, n=3). DA concentrations plotted against time in 20-minute bins. ***C***, From 700 minutes to 880 minutes, during active responding for cocaine, the defeat-experienced rat (red, n=1) displayed a higher average DA concentration compared to non-defeat-experienced controls (white, n=3). DA concentrations plotted against time in 20-minute bins.

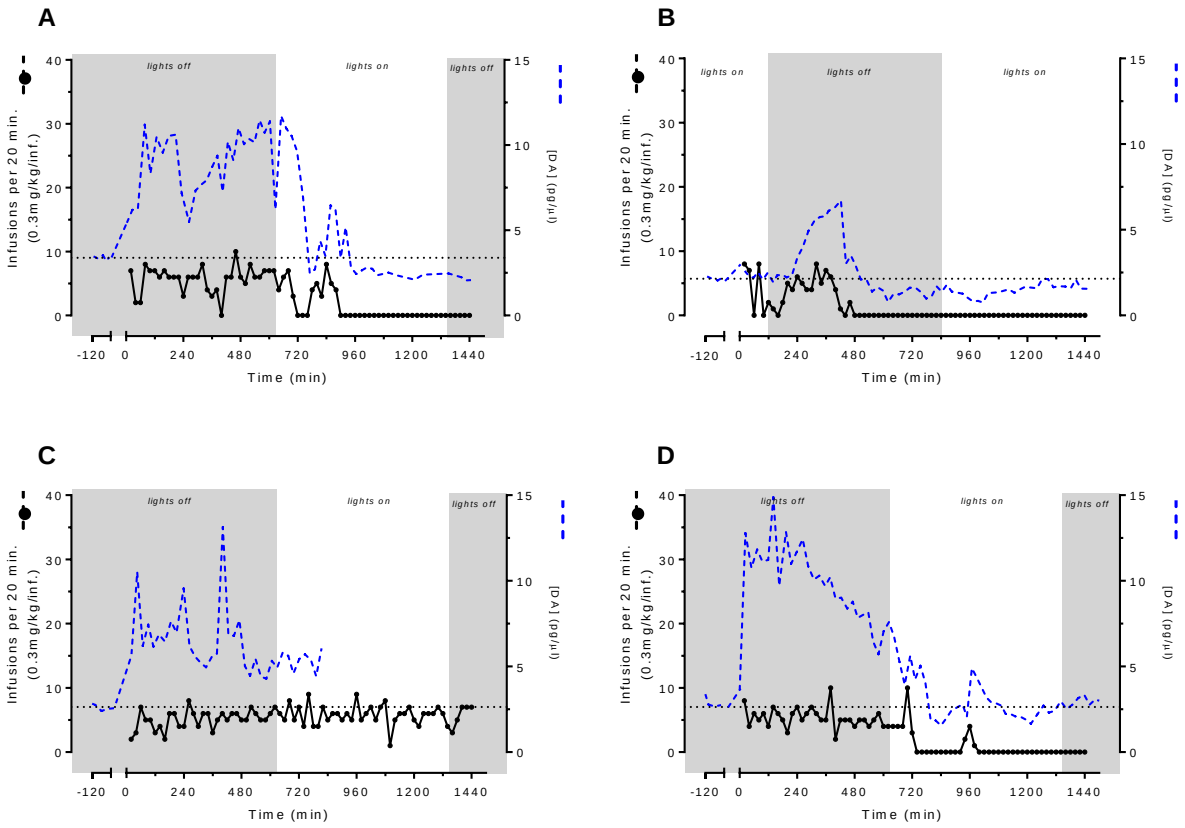

Figure 8.

Time course of cocaine self-administration and DA concentrations over 24-hour binge. Changes in response rate for cocaine corresponded well to the observed fluctuations in DA levels across stress conditions. ***A***, Control animal #576 ***B***, Control animal #608 ***C***, Control animal #653 ***D***, Control animal #692.

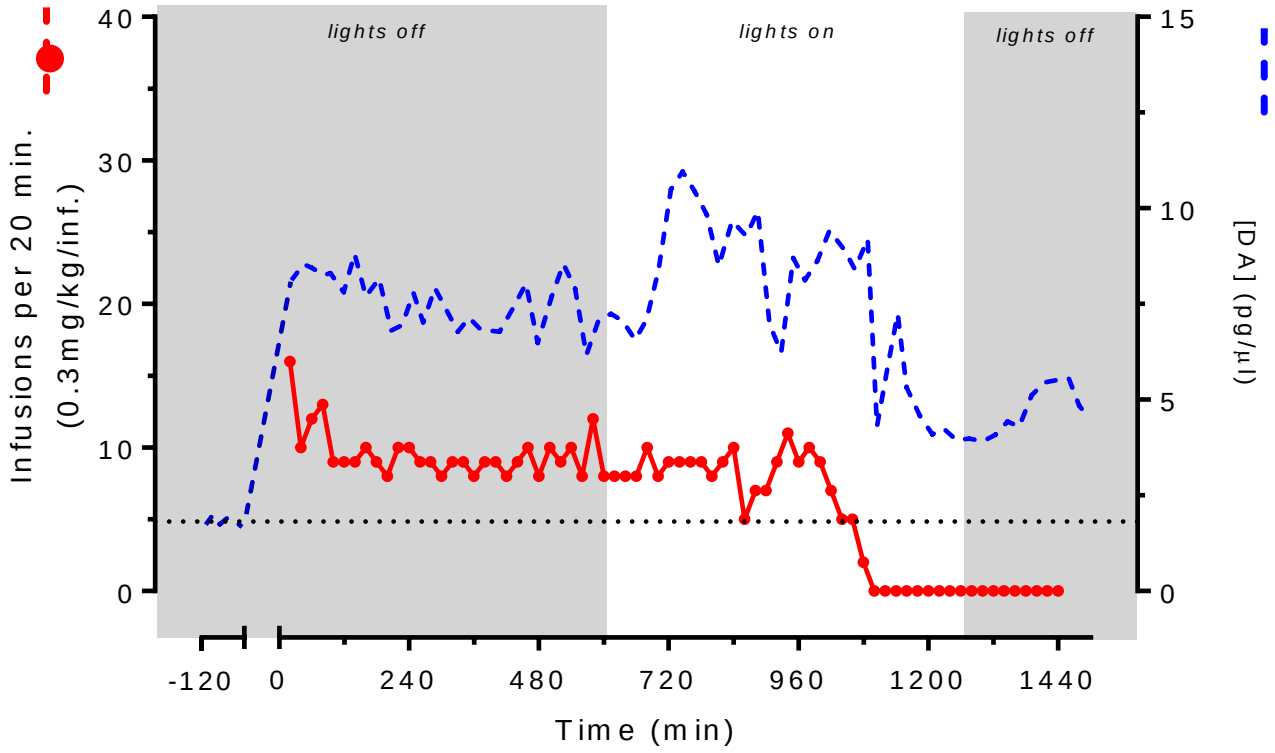

Figure 9.

Time course of cocaine self-administration and DA concentrations over 24-hour binge. Changes in response rate for cocaine corresponded well to the observed fluctuations in DA levels across stress conditions. Defeat animal #603.

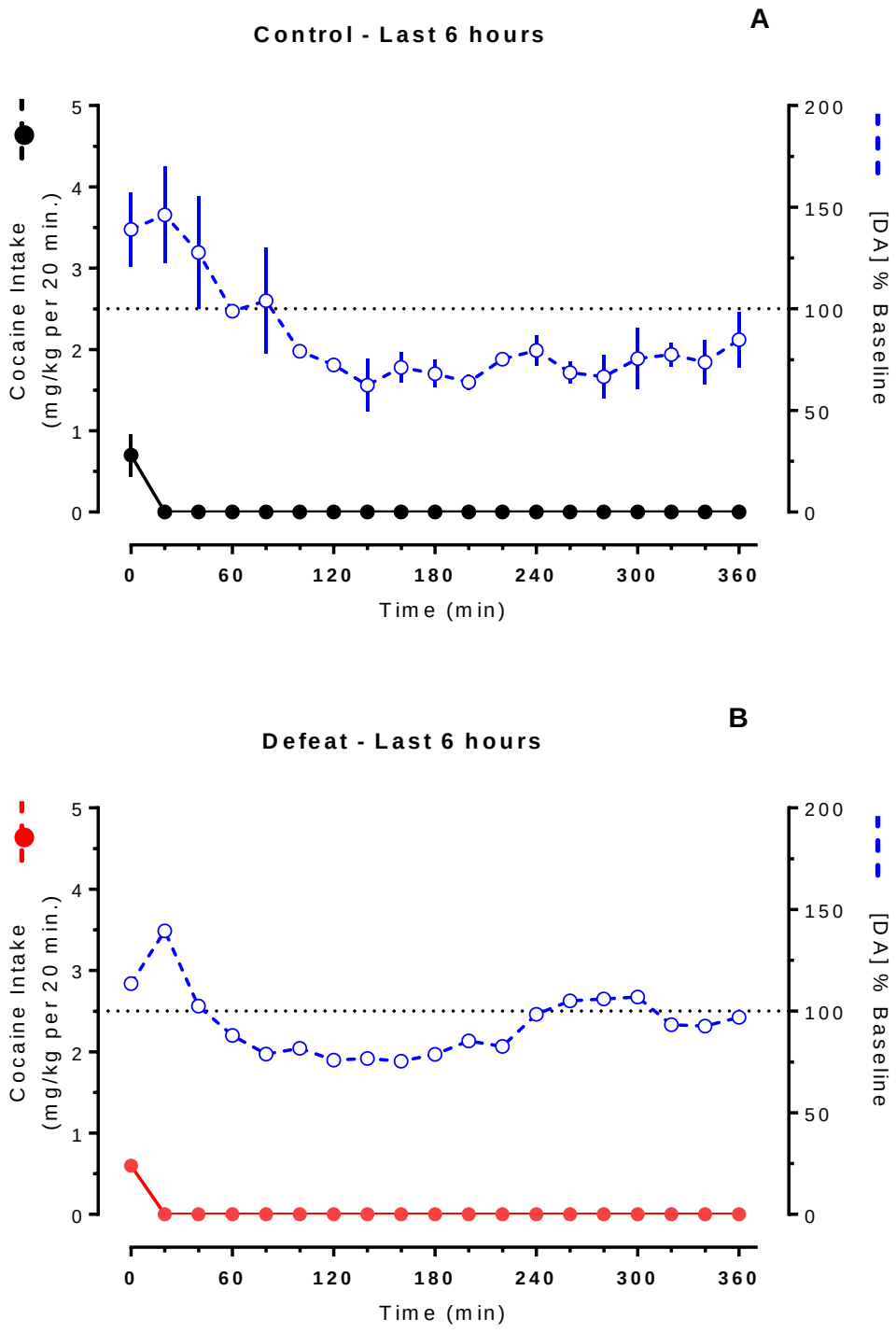

Figure 10.

Time course of cocaine self-administration and DA concentrations over 24-hour binge (Last 6 hours). All animals showed a prolonged undershoot of DA following termination of self-administration. ***A***, Averaged control animals, depression lasted 240 minutes and never recovered to baseline levels. ***B***, Defeat animal, depression lasted 180 minutes before returning to higher baseline levels.

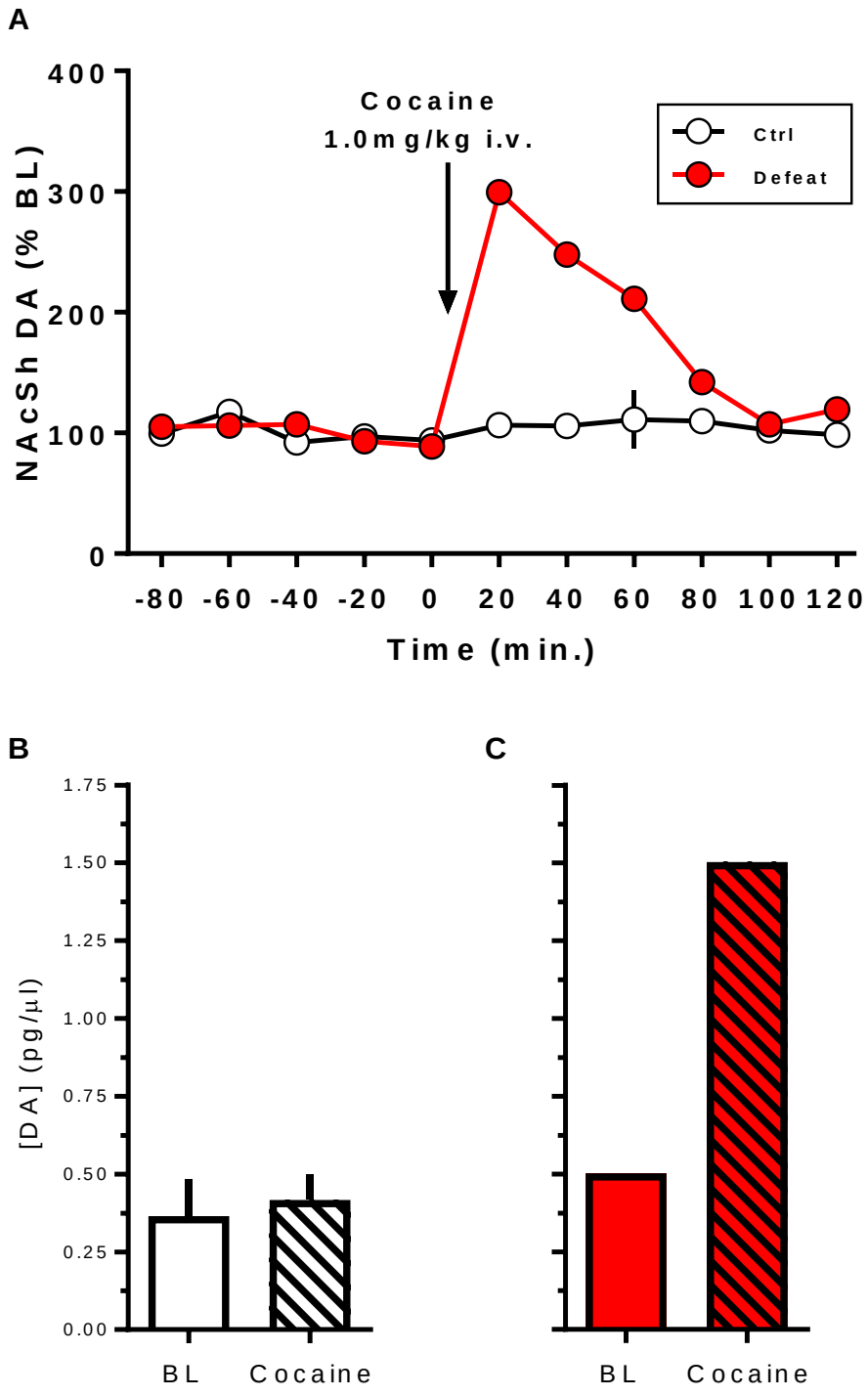

Figure 11.

A, Time course of cocaine challenge and elicited DA concentrations. A 1.0 mg/kg dose of IV cocaine did not elicit an increase in DA concentration on control animals (***B***) but did elicit an increase in DA concentration in the defeat-experienced animal (***C***).

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