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Stress modulation of drug self-administration: implications for addiction comorbidity with post-traumatic stress disorder

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Abstract

Drug abuse and dependence present significant health burdens for our society, affecting roughly 10% of the population. Stress likely contributes to the development and persistence of drug use; for example, rates of substance dependence are elevated among individuals diagnosed with post-traumatic stress disorder (PTSD). Thus, understanding the interaction between stress and drug use, and associated neuroadaptations, is key for developing therapies to combat substance use disorders. For this purpose, many rodent models of the effects of stress exposure on substance use have been developed; the models can be classified according to three categories of stress exposure: developmental, adult nonsocial, and adult social. The present review addresses preclinical findings on the effect of each type of trauma on responses to and self-administration of drugs of abuse by focusing on a key exemplar for each category. In addition, the potential efficacy of targeting neuropeptide systems that have been implicated in stress responses and stress system neuroadaptation in order to treat comorbid PTSD and substance abuse will be discussed.

1. Introduction

Substance abuse and addiction cause significant health care burdens on society, with current estimates suggesting 10% of the population suffers from some form of substance use disorder (Hall et al., 1999; Ross, 1995; Stinson et al., 2005). The progression of drug abuse has been depicted as a downward spiral comprised of three stages: binge/intoxication, preoccupation/anticipation, and withdrawal/negative affect (Koob and Le Moal, 1997). During the acquisition phase, characterized by episodes of intoxication, drug taking produces positive reinforcement. With the development of drug dependence, withdrawal leads to a negative emotional state; as a result, drugs are taken to alleviate or avoid withdrawal symptoms (i.e., negative reinforcement). Periods of abstinence are characterized by pervasive thoughts about the addictive drug, yielding a high rate of relapse (Koob et al., 2004). Brain stress systems are thought to play a significant role in generating the negative emotional state characteristic of drug dependence, with dysregulation of stress systems also underlying the persistence of drug-seeking and relapse (Koob, 2008). The recruitment of brain stress systems during the progression to drug dependence suggests that anxiety disorders, characterized by heightened stress responses, may predispose individuals to

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develop addictive disorders and/or perpetuate and worsen addictive disorders once established.

One anxiety-related disorder receiving increased attention as a possible contributing factor to the development of addictive disorders in humans is post-traumatic stress disorder (PTSD). Triggered by exposure to a traumatic experience, PTSD is characterized by persistent maladaptive symptoms related to the trauma, including blunted emotional responses, hyperarousal, and flashbacks. Among individuals diagnosed with PTSD, the incidence of drug abuse and addiction is markedly elevated, with the highest comorbidity observed for alcohol dependence, followed by other depressants, such as opioids and cannabinoids, although stimulants like cocaine are also abused by some, possibly dependent on the sequelae of symptoms experienced by the individual (Jacobsen et al., 2001). Multiple studies have shown three- to five-fold increases in the development of substance abuse among PTSD patients, yielding substance abuse comorbidity in nearly half of all PTSD patients (Breslau et al., 2003; Mills et al., 2006; Perkonigg et al., 2000). Conversely, upwards of 25% of the substance abusing population may suffer from some form of PTSD (Driessen et al., 2008). Even in the absence of PTSD, traumatic experiences can precipitate relapse in recovering addicts (Dewart et al., 2006; Zywiak et al., 2003). Individuals with substance abuse disorders with comorbid PTSD face worse treatment outcomes (Brown et al., 1995; Brown and Wolfe, 1994), indicating a need for improved therapies to address the dual diagnosis. Thus, understanding the neural mechanisms that may jointly subserve PTSD and substance abuse presents an important target for therapeutic development.

Several animal models have been established that resemble key phenotypes of PTSD, such as long-term persistence of conditioned fear responses and heightened sensitivity to novel stressful stimuli. Such paradigms include delivery of electric shocks to tail or paws, social stress from exposure to predators or aggressive conspecifics, or multiple stressors experienced one after the other, termed single prolonged stress (Stam, 2007). Lack of predictability and controllability of the stressors are central features of paradigms that generate persistent post-traumatic effects (Foa et al., 1992; Koolhaas et al., 2011). While not fully validated as rodent models of PTSD, early life traumas, such as maternal separation, can have long-lasting effects on adult stress responsiveness, including heightened startle and novelty responses, hypothesized to be key elements of rodent PTSD models (Kalinichev et al., 2002a; Kalinichev et al., 2002b). Exposure to social and nonsocial stressors in adulthood has been used to model how adult traumatic stress alters behavior, both acutely and following extended post-stress intervals. Social stressors, such as isolated housing and defeat by a dominant animal, rely on the innate sociability and social structures of the animals in question. Numerous paradigms exist to generate nonsocial stress, including restraint, forced swimming, tail pinch, and electric shock. Chronic variable stress may utilize both varieties of adult stressors, as it involves sequential exposure to multiple stressors over time. Although published studies have not explicitly investigated the interaction between a PTSD-like state and drug self-administration, many have utilized stress delivery paradigms in the context of drug self-administration that have otherwise been verified to generate PTSD-like symptoms in rodents.

This review focuses on rodent models designed to test the effects of stressors on motivational properties of alcohol and drugs of abuse. The interaction between stressful life events and drug addiction will be analyzed by focusing on one prototypical stressor from each category – maternal separation, footshock and social defeat as models of early life, adult nonsocial and adult social stress – and their ability to modulate rodent behavioral responses to and self-administration of drugs of abuse. The studies discussed below highlight the dual temporal impact of stressors, which can both acutely precipitate behavioral changes and exert effects following an extended post-stress interval, as is

characteristic of PTSD (Figure 1). It should be noted, however, that none of the studies has directly addressed the generation of a PTSD-like state in the rodent on drug self-administration, and thus the intention is not to validate the existing paradigms as rodent models of comorbid PTSD and drug abuse. Instead, synthesis of the current knowledge regarding stress modulation of rodent drug self-administration, as well as pharmacological targets showing promise for decreasing drug self-administration in these models, may provide a foundation for the future development of behavioral paradigms that more directly address the role of trauma in modulating drug use, as well as the efficacy of new pharmacotherapies to treat comorbid PTSD and drug abuse.

2. Effects of early life trauma: maternal separation

Stress experienced early in life can profoundly affect adult behavior, with childhood trauma associated with the severity of drug dependence (Enoch et al., 2010; Triffleman et al., 1995). One common model of early life traumatic stress in rodents is maternal separation, a paradigm involving repeated separation of pre-weaning pups from their mothers (Lehmann and Feldon, 2000; Plotsky and Meaney, 1993). The effects of maternal separation depend on the length of separation, as brief (15-minute) separation may be protective from, and extended (>180 minute) separation predisposing to, heightened stress responses (Plotsky and Meaney, 1993). Extended maternal separation results in increased anxiety-like behavior in adult rats (Huot et al., 2001; Kalinichev et al., 2002b; Romeo et al., 2003), as well as elevated startle responses (Caldji et al., 2000), indicative of the face validity of maternal separation as a model for early life trauma yielding PTSD-like symptoms in adulthood. In humans, newborns that required isolation from their mothers during the first few months of life for medical reasons had increased risk of developing drug dependence (Veijola et al., 2008). Thus maternal separation provides a plausible model for studying the protracted effects of childhood trauma on drug self-administration in rodents.

2.1 Alcohol

A history of maternal separation dose-dependently alters alcohol self-administration in adulthood; that is, the duration of the maternal separation directly impacts its modulation of alcohol drinking. Brief, 15-minute daily separations of the litter from the dam, often referred to as “handling,” reduced two-bottle choice alcohol intake, as compared with non-handled controls, in male rats from multiple strains (Hilakivi-Clarke et al., 1991; Jaworski et al., 2005; Ploj et al., 2003), including the alcohol-preferring Alko alcohol (AA) rats (Roman et al., 2003). Handling also reduced the acquisition rate of two-bottle drinking in AA rats, suggesting that brief intervals of maternal separation may protect against the development of high alcohol intake in rats otherwise prone to excessive alcohol consumption.

Unlike brief exposure, extended maternal separation increased alcohol intake in adulthood. Moderate, 3-hour neonatal separation elevated sweetened 10% alcohol intake in adult mice (Cruz et al., 2008). Rats with similar extended separation histories also drank significantly more sweetened alcohol in adulthood than handled rats, although results varied in comparison to control rats, with maternally separated rats showing either significant increases (Huot et al., 2001) or no significant difference (Jaworski et al., 2005) in alcohol intake. Increasing the duration of separation to 6 hours yielded elevated adult alcohol intake compared with both handled and control rats (Ploj et al., 2003). This effect was less pronounced in AA rats, which displayed higher alcohol consumption than handled, but not control, rats despite having experienced 6-hour intervals of maternal separation (Roman et al., 2003). Interestingly, while males show altered alcohol intake following maternal separation, most data suggest lesser effects of maternal separation in female rats (Roman et al., 2005; Roman et al., 2004). Taken together, the data indicate that, in rodents, brief maternal separation may generate resilience against the development of alcohol addiction,

while prolonged neonatal separations may dose-dependently contribute to elevated alcohol intake in adulthood. To date, little data exist on the role neonatal stress history may play in relapse to alcohol drinking; however, given that maternal stress promotes an anxiety-like state (Huot et al., 2001; Kalinichev et al., 2002b; Romeo et al., 2003) and heightened alcohol consumption in the adult offspring (Cruz et al., 2008; Huot et al., 2001; Ploj et al., 2003; Roman et al., 2005; Roman et al., 2003), elevation of both reinstatement and relapse-like responding might be predicted.

2.2 Psychostimulants

Maternal separation also differentially modulates adult responses to psychostimulants, in relation to the severity of the maternal separation history. Neonatal handling blunted male rats' locomotor responses to acute doses of cocaine (Brake et al., 2004), and handling decreased adult cocaine self-administration under a fixed ratio schedule to saline-like levels across all doses tested (Moffett et al., 2006). The rats still showed preference for the cocaine-paired (vs. inactive) lever, and responses during initial food training were not different from other groups, suggesting that the low response was not due to impaired task acquisition (Moffett et al., 2006). Handling also reduced male rats' sensitivity to the rewarding effects of amphetamine in adulthood, resulting in blunted preference for the previously drug-paired chamber in a conditioned place preference (CPP) test (Campbell and Spear, 1999). Together, the results indicate that, in rodents, brief maternal separation may confer protection against the development of psychostimulant dependence by reducing the drugs' rewarding and activating potency.

In contrast to brief separation, longer maternal separation periods enhance the activating and reinforcing properties of psychostimulants in adulthood. Mice with a history of extended maternal separation displayed elevated locomotor sensitization to cocaine (Kikusui et al., 2005), although this effect was not observed after amphetamine treatment in rats (Weiss et al., 2001). Extended maternal separation also facilitated the acquisition of cocaine self-administration at a low per-infusion unit dose – one that did not otherwise support self-administration in non-handled or briefly handled rats. The results suggest a heightened sensitivity to the reinforcing effects of low doses of cocaine results from extended maternal separation (Moffett et al., 2006). Extended maternal separation also enabled rats to discriminate between the cocaine-paired and inactive levers, a behavioral selectivity not observed in control groups (Moffett et al., 2006). Additional research demonstrated that acute amphetamine treatment reduced threshold currents for intracranial self-stimulation (ICSS) of the lateral hypothalamus to a greater degree in rats with a history of maternal separation than in controls (Der-Avakian and Markou, 2010), indicative of enhancement of the facilitatory effect of psychostimulants on brain reward function following a history of extended maternal separation. It should be noted that Robbins and colleagues showed reductions in both amphetamine-induced hyperactivity (Matthews et al., 1996) and cocaine self-administration on the first day of acquisition (Matthews et al., 1999) in rats with a history of maternal separation. The rats also showed no change in amphetamine-induced reductions in lateral hypothalamic ICSS thresholds (Matthews and Robbins, 2003). However, the Matthews and Robbins study involved more sporadic delivery and later onset of maternal separation than most other studies cited, with separation occurring on 10 randomly selected days between postnatal days 5 and 20, rather than daily for the first 2–3 weeks of life. Thus the discrepancy between results may arise from reduced severity of the maternal separation when delivered more infrequently or outside a critical period of development. Regardless, the balance of the data supports the hypothesis that lengthy maternal separation elevates responsiveness to and propensity to self-administer psychostimulants in adulthood.

Reinstatement of psychostimulant-seeking may also be modulated by a history of maternal separation. Zhang and colleagues (2005) found no significant alteration of cocaine-induced reinstatement in adult rats that had experienced 1-hour maternal isolation, a paradigm involving not only maternal separation but also isolation from littermates. However, the same isolation paradigm yielded increased cue-induced reinstatement (Lynch et al., 2005). Additional studies using maternal separation and brief handling are required to fully understand the impact of neonatal handling on reinstatement responding; nonetheless, the existing data suggest that early postnatal maternal separation in rodents may have a lasting impact not only on drug response and intake in adulthood but also on the magnitude of relapse to drug-seeking after periods of abstinence.

2.3 Opiates

While fewer studies have investigated the effects of maternal separation on the activating and reinforcing properties of opiates, the available data suggest similarities to the results described for alcohol (Section 2.1) and psychostimulants (Section 2.2). Three-hour neonatal maternal separation sessions resulted in increased locomotor sensitization to morphine as well as elevated morphine CPP in adult male rats (Kalinichev et al., 2002a; Michaels and Holtzman, 2008). Maternal separation also increased rats' sensitivity to the acute modulation of lateral hypothalamus ICSS thresholds by heroin, with threshold elevations, normally observed only after high–dose exposure, occurring at moderate doses in rats with a history of maternal separation (Matthews and Robbins, 2003). In addition, when the rats were made dependent on morphine, those with a history of maternal separation showed elevated somatic withdrawal scores (Kalinichev et al., 2001). Together the data suggest that maternal separation not only enhances the acute activating and reinforcing properties of opiates, but may increase sensitivity to the drugs' dependence-associated hypohedonic effects.

2.4 Summary

As detailed in Sections 2.1–2.3, maternal separation enhances sensitivity to and self-administration of multiple drugs of abuse in adulthood. These data are consistent with human studies indicating a relationship between childhood trauma and drug dependence in adulthood (Enoch et al., 2010; Hyman et al., 2008; Triffleman et al., 1995; Veijola et al., 2008). Maternal separation therefore may provide a valid model for investigation of therapeutic interventions for treatment of drug addiction in patients with a history of childhood trauma.

3. Effects of adult nonsocial stress: footshock

Many paradigms that involve delivery of mild physical stressors to adult rodents trigger anxiety-like behavior suggestive of a stress-like state. One of the most commonly used methods of stress delivery in rodents is footshock, the primary stimulus for aversive Pavlovian conditioning in rodents. Footshock provides a discretely manipulatable stressor, as duration, frequency, intensity, predictability, and controllability of the stress presentation can all be regulated. As discussed elsewhere, several paradigms of inescapable shock delivery in unpredictable patterns have been shown to create a PTSD-like state in rodents (Foa et al., 1992; Garrick et al., 1997; Maier, 2001; Pynoos et al., 1996; Rau et al., 2005; Siegmund and Wotjak, 2007), supporting the face validity of this model for providing useful information regarding the effects of traumatic stress on drug self-administration. Unlike maternal separation, which is by nature temporally removed from adult drug self-administration, footshock stress delivered to the adult animal allows for determination of the temporal relationship between stress exposure and alterations in drug self-administration, as both precipitant (immediate) and post-traumatic (delayed) effects of footshock exposure can be investigated.

3.1 Alcohol

Footshock has varying effects on alcohol intake, having been found to increase (Caplan and Puglisi, 1986; Casey, 1960; Chester et al., 2008; Funk et al., 2004; Matthews et al., 2008; Mills et al., 1977; Opsahl and Hatton, 1972; Vengeliene et al., 2003; Volpicelli et al., 1986; Volpicelli and Ulm, 1990; Volpicelli et al., 1990), have no effect (Brunell and Spear, 2005; Chester et al., 2008; Fidler and LoLordo, 1996; Myers and Holman, 1967) and decrease (Brunell and Spear, 2005; Caplan and Puglisi, 1986; Dayas et al., 2004) alcohol intake. The discrepancies between these studies may stem from key differences in stress delivery (Table 2), alcohol access, and housing conditions, demonstrating the importance not only of the stress delivery but also of stress cues in modulating alcohol intake. In particular, living continuously in the shock delivery chambers tended to suppress the rats' consumption of all fluids, including alcohol, during the shock delivery period (Caplan and Puglisi, 1986; Casey, 1960; Opsahl and Hatton, 1972), except in cases where cues signaled the approach of uncontrollable shock delivery (Cicero et al., 1968; Opsahl and Hatton, 1972). For rats returned to live in a safe environment after the completion of footshock exposure, alcohol intake increased over the period following the termination of shock, generally reaching significantly elevated levels within the first 24–48 hours, an effect observed both in mice (Matthews et al., 2008; Racz et al., 2003) and rats (Caplan and Puglisi, 1986; Vengeliene et al., 2003) (but see also Dayas et al., 2004). Elevations in alcohol preference tended to be more delayed for rats living in the shock environment, with increased intake commencing anywhere from 24 hours (Volpicelli and Ulm, 1990) to 1 week (Casey, 1960) after termination of footshock. Even in the absence of heightened cumulative alcohol intake, analysis of drinking patterns during shock presentations indicated that alcohol intake clustered in the immediate post-shock interval for rats living in the shock chambers (Mills et al., 1977). Casey (1960) observed a prolonged increase in alcohol intake that peaked 2 weeks after the final footshock, suggestive of protracted-onset, long-term alterations in alcohol intake due to a history of footshock exposure. Together, these data indicate that footshock stress may not only increase alcohol consumption in the immediate post-stress interval but also have longer lasting effects.

In addition to modulating maintenance drinking, footshock can also acutely alter alcohol-related behaviors following a period of abstinence, as seen in stress-induced reinstatement models. Footshock reinstated operant responding on a previously alcohol-paired lever in the absence of reinforcement when delivered to rats in the 5- to 15-minute period prior to the operant session (Le et al., 2002; Le et al., 1998). Delivery of cues previously paired with alcohol during the reinstatement session further enhanced the alcohol-seeking triggered by footshock stress (Liu and Weiss, 2002). The reviewed experiments demonstrate that stressors may acutely trigger elevated alcohol seeking; however, they do not address the ability of stressful situations to create a long-lasting propensity to relapse. One series of studies beginning to address that issue utilized cues previously paired with footshock and alcohol delivery to successfully reinstate alcohol-seeking more than a month after the last alcohol-cue pairing and 5 days after the final footshock conditioning session (Liu and Weiss, 2003). Neither cue independently reinstated operant responding in nondependent rats, but co-presentation of the cues significantly elevated responding on the previously alcohol-paired lever. These effects were heightened in rats with a history of alcohol dependence, in which both the footshock and alcohol cues elevated operant responding independently and to an even greater degree when presented together (Liu and Weiss, 2003). These data demonstrate that stressful experiences or situational reminders can precipitate alcohol-seeking, and these effects are more prominent in subjects with a history of alcohol dependence.

3.2 Psychostimulants

Uncontrollable footshock enhanced the locomotor effects of acute amphetamine and cocaine injections delivered the following day, as demonstrated by enhanced stereotypic behaviors in rats with a history of footshock stress (MacLennan and Maier, 1983). Given its ability to modulate the acute response to psychostimulants, footshock might be predicted to modify acquisition of psychostimulant self-administration. Acquisition of cocaine self-administration was enhanced by noncontingent footshock presentations delivered during 1-hour food self-administration sessions immediately preceding cocaine self-administration, with rats demonstrating task learning at lower doses and attaining higher overall cocaine intake than controls (Goeders and Guerin, 1994). The authors also demonstrated the importance of uncontrollability of the footshocks, as rats with the ability to terminate their footshocks did not escalate their self-administration. Because footshocks were delivered for at least 9 days prior to the onset of cocaine self-administration training and throughout the acquisition period, it cannot be determined whether the observed effects were due to acute effects of footshock exposure or to the extensive history of stress exposure. Using different training procedures, Ramsey and Van Ree (1993) found that exposure to footshock just prior (15 min) to self-administration elevated responding for cocaine only on the first day of acquisition, an effect not observed for amphetamine self-administration (Moffett and Goeders, 2005). Rats forced to observe footshock delivery to conspecifics displayed an increased rate of acquiring cocaine self-administration across the entire acquisition period (Ramsey and Van Ree, 1993). Thus, either footshock stress itself or the psychosocial experience of witnessing footshock of a conspecific may elevate acquisition of psychostimulant self-administration. The effects of footshock are not confined to acquisition, however. Daily exposure to 4 alternating blocks of 5-minute footshock stress and 30-minute cocaine self-administration triggered a significant escalation in cocaine intake within three days of the first footshock exposure and lasted for the remainder of the 14-day experimental period, during which time rats continued to experience alternating footshock/self-administration sessions (Mantsch and Katz, 2007). These studies indicate that exposure to footshock can elevate both acquisition and maintenance levels of cocaine intake, although further investigation is required to differentiate between the short- versus long-term effects of footshock stress on psychostimulant self-administration.

Like acquisition and maintenance, reinstatement of operant responding or CPP for psychostimulants can be precipitated by footshock stress (stress-induced reinstatement). Intermittent footshock exposure prior to operant sessions elevated responding on the lever previously paired with cocaine in rats (Erb et al., 1996), an effect that did not generalize to responding for food (Ahmed and Koob, 1997) or sucrose (Le et al., 1998). These effects were often observed immediately after the footshock conditioning session, although the reinstating effects of acute footshock were shown to persist for up to 40 minutes after a single session of intermittent footshock (Brown and Erb, 2007). As previously described for alcohol (Section 3.1), footshock and cocaine-paired cues function additively in reinstatement of cocaine-seeking in rats (Buffalari and See, 2009). The reinstating effect of footshock stress is not restricted to operant drug-seeking, however, but also applies to preference for a drug-paired environment. Administration of 15-minute footshock sessions prior to CPP testing reinstated preference for the previously cocaine-paired chamber in mice (Redila and Chavkin, 2008) and rats (Wang et al., 2000). Discrete footshock-conditioned cues also reinstated cocaine CPP in rats, despite several weeks' delay between fear conditioning and reinstatement testing (Sanchez and Sorg, 2001). Together these data suggest that traumatic stressors such as footshock, or even conditioned reminders of the stress, can trigger psychostimulant-seeking in otherwise abstinent individuals.

3.3 Opiates

Fewer studies have investigated the effects of footshock stress on opiate self-administration. However, the existing literature resembles the findings discussed above for alcohol (3.1) and psychostimulants (3.2). Footshock immediately prior to heroin self-administration sessions resulted in enhanced responding for high doses of heroin on a progressive ratio schedule (Shaham and Stewart, 1994); that is, footshock increased the amount of work rats would perform for each additional dose of heroin. As with cocaine, the emotional stress of observing footshock heightened morphine self-administration in mice, including in mice that demonstrated no difference in self-administration of morphine and saline prior to stress exposure (Kuzmin et al., 1996). These data support a role for footshock stress in acutely upregulating opiate intake.

Footshock also acutely reinstated preference for a chamber formerly paired with morphine (Wang et al., 2000) as well as operant responding on a lever that previously delivered heroin (Shaham et al., 1996) in rats. Reinstatement of self-administration was observed not only under standard drug-free test conditions but even when heroin levels were maintained throughout extinction and reinstatement via a minipump delivering constant infusions of heroin (Shaham et al., 1996). This finding suggests that acute stress-induced elevations in heroin-seeking are not driven solely by the desire to regain the pre-extinction pharmacological effects of heroin. However, that does not mean that reinstatement following footshock is independent of pre-extinction self-administration levels. Rats provided extended daily access to heroin self-administration during training, which results in escalation of heroin self-administration, showed significantly greater footshock-induced reinstatement than did rats that received brief daily access and whose heroin self-administration had not escalated (Ahmed et al., 2000). Together, the data indicate that acute footshock stress can precipitate relapse to heroin self-administration, and that the severity of the relapse may directly correspond to the amount of drug taken prior to abstinence.

3.4 Summary

Footshock has been used as a stressor in several rodent models of PTSD (Foa et al., 1992; Garrick et al., 1997; Maier, 2001; Pynoos et al., 1996; Wakizono et al., 2007) and thus provides a plausible model for the effects of adult traumatic experiences on drug self-administration. All phases of drug self-administration – acquisition, maintenance, and relapse – were acutely elevated in rats recently exposed to footshock stress, and these effects were observed across all drugs of abuse tested. However, most stress delivery paradigms addressed the acute, rather than protracted, consequences of footshock exposure, and thus these data fail to address PTSD-like delayed effects of traumatic stress. As existing data suggest that behavioral responses to and self-administration of drugs of abuse are elevated in the weeks following exposure to multiple psychological stressors (Table 1), additional research into the role of stress history, rather than stress delivery, on drug self-administration is warranted. Nonetheless, acute footshock-induced modulation of drug-taking presents a useful model for investigating pharmacologic tools for treatment of comorbid drug and anxiety disorders.

4. Effects of adult social psychological stress: social defeat

Anxiety-provoking social encounters can precipitate increased alcohol intake in both dependent (Miller et al., 1974) and nondependent (de Wit et al., 2003) human subjects, and social phobia is a significant predictor of future alcohol dependence (Kessler et al., 1997). One rodent model of social stress is the social defeat paradigm, in which a territorial resident rat or mouse confronts and dominates an intruder (Miczek et al., 2008). Aggressive social interactions, such as muggings, rape, and physical abuse, can trigger the development of

PTSD in humans, suggesting reasonable face validity for the social defeat model. Thus, alterations in behavior, including modulation of drug intake, following one or more experiences of subordination provide insight into the persistent effects of socially stressful experiences as well as a mechanism for testing possible therapies.

4.1 Alcohol

In rodents, alcohol consumption is regulated by social hierarchies in group-housing situations, with submissive rats (Blanchard et al., 1987) and mice (Hilakivi-Clarke and Lister, 1992) consuming higher quantities of alcohol than their dominant cage mates. Thus, it would be predicted that the experience of defeat, which engenders subordination in the intruder rat, should elevate alcohol intake. However, as with footshock exposure (Section 3.1), the modulation of alcohol consumption by social defeat stress varies under different experimental paradigms. Studies by van Erp and colleagues demonstrated decreased home cage 10% alcohol intake on all days that rats experienced social defeat immediately preceding or coincident with alcohol access (van Erp and Miczek, 2001; van Erp et al., 2001), regardless of whether alcohol access was brief (15 min) or continuous. Similarly, under operant access conditions, rats self-administered less alcohol on defeat days when the defeat session immediately preceded the operant session, although intake levels recovered within 1–2 days of the final defeat exposure (Funk et al., 2005; van Erp and Miczek, 2001). The reduction in operant alcohol self-administration following social defeat abates as the temporal delay between defeat and self-administration sessions increases, with no significant change in 15% alcohol self-administration observed 4 or 24 hours after defeat exposure (van Erp and Miczek, 2001). However, on the day after the final defeat exposure, rats trained with a 4-hour interval between defeat and operant sessions showed a significant elevation in alcohol intake, suggesting persistent effects of a history of social stress (van Erp and Miczek, 2001). Milder, 5-minute defeat exposure paradigms have yielded different results, with modest elevation of home cage 6% alcohol consumption observed both the week of and the week after stress exposure when alcohol access was provided 2 hours after the defeat session (Caldwell and Riccio, 2010). Repeated, but not single, mild social defeat encounters did not alter home cage 8% alcohol intake on defeat days but rather yielded increased alcohol intake in the second week after defeat exposure (Croft et al., 2005). Together, these data suggest a temporal delay in the upregulation of alcohol intake following social stress exposure.

Relapse-like alcohol intake and reinstatement of alcohol-seeking behavior, similar to maintenance alcohol consumption, respond variably to social defeat stress. Repeated episodes of defeat exposure, delivered over a 2-week alcohol deprivation period, elevated alcohol drinking in rats upon renewed access (Funk et al., 2004). However, unlike footshock stress, which can trigger reinstatement of alcohol-seeking when delivered immediately prior to the operant session (Section 3.1), acute social defeat did not significantly alter rats' activity at the previously alcohol-paired lever (Funk et al., 2005). Nonetheless, when rats were conditioned to associate social defeat with an odor cue, the presentation of the odor cue alone reinstated operant responding (Funk et al., 2005). Together, these data demonstrate that while social stress may acutely suppress both ongoing intake and relapse to alcohol self-administration, a history of social defeat stress and situational reminders of the stress may, over time, result in elevated alcohol intake.

4.2 Psychostimulants

Similar to other stressors applied in adulthood, social defeat enhances locomotor responses to amphetamine and cocaine (Covington et al., 2005; Covington and Miczek, 2001; Miczek et al., 1999; Nikulina et al., 1998; Yap and Miczek, 2007). Perhaps due to this heightened response, social defeat stress occurring 24 hours (Tidey and Miczek, 1997) or 1 week

(Haney et al., 1995) prior increased the rate of acquisition of cocaine self-administration. Defeat immediately prior to operant sessions also increased cocaine self-administration (Miczek and Mutschler, 1996). With increased delays between social defeat exposure and cocaine self-administration training, effects of stress history on acquisition dissipated (Covington et al., 2005; Covington and Miczek, 2001); instead, elevated self-administration was observed during later 24-hour binge sessions (Covington et al., 2005; Covington and Miczek, 2001, 2005; Cruz et al., 2011). Certain subpopulations may be more susceptible to social defeat's effects on cocaine self-administration. For example, rats that exhibit reduced locomotor activity in novel environments self-administer low levels of cocaine initially. Social defeat subsequently elevated their self-administration to the level of high novelty response rats, whose high baseline cocaine self-administration levels, in contrast, were insensitive to stress history (Kabbaj et al., 2001). Interestingly, acute defeat, administered immediately prior to lateral hypothalamic ICSS sessions, elevated response thresholds (Der-Avakian and Markou, 2010). This increase in thresholds suggests that social defeat impairs brain reward function. Together, these data demonstrate that social defeat stress heightens behavioral activation by psychostimulants and self-administration of psychostimulants, with effects dependent on the temporal contingency between the defeat and psychostimulant experiences. In addition, social stress may differentially escalate drug intake in individuals that would otherwise be less prone to psychostimulant dependence, possibly by altering the drugs' reinforcing efficacy.

Little research has investigated the role of social defeat in the reinstatement of psychostimulant-seeking behaviors. One study investigated the effect of acute social defeat on reinstatement of CPP in the presence of a low dose of cocaine (Ribeiro Do Couto et al., 2009). The authors found greater reinstatement of preference for the previously cocaine-paired chamber in recently defeated mice than in controls. This effect may depend on both the defeat experience and the cocaine prime, as the lowest unit cocaine doses administered did not significantly reinstate cocaine CPP. Nonetheless, in light of the upregulation of psychostimulant self-administration following social stress, the results warrant further investigation into the effects of social stress on relapse to psychostimulant-seeking.

4.3 Opiates

Investigation of the impact of social stress on opiate-related behaviors has lagged behind that for alcohol and psychostimulants. Most studies thus far have focused on the rewarding effects of opiates as determined by conditioned preference for an opiate-paired environment. Exposure to defeat prior to place conditioning demonstrated an interaction between social defeat exposure and pre-existing social status in socially housed mice (Coventry et al., 1997). Under control conditions, subordinate mice failed to show preference for a morphine-paired environment, while dominant rats spent significantly more time in the drug-paired chamber. However, a history of defeat reversed these effects, with defeated subordinate mice displaying significant morphine CPP, while dominant mice rendered subordinate by their defeat experiences no longer expressed conditioned preference. In a separate study, social defeat reinstated extinguished morphine CPP in mice tested either immediately or 15 minutes after the defeat experience (Ribeiro Do Couto et al., 2006). Together, these studies suggest that acute social defeat stress may interact with the rewarding properties of morphine, and that perceived social status may modulate the effect of social stressors on opiate response. However, a recent study involving operant self-administration of heroin, with operant training beginning nearly 2 weeks after social defeat, showed no difference in either acquisition or binge-like 24-hour self-administration of heroin (Cruz et al., 2011). In light of the correlation between CPP and self-administration of opiates following footshock stress (Section 3.3), further investigation is required to determine whether, under different conditions, social stress may trigger elevated opiate self-administration.

4.4 Summary

Social stress, which can increase drug intake in humans, has been modeled in rodents as defeat in a resident-intruder paradigm. Similar to social stress effects in humans, both acute and repeated social defeat exposure enhanced ongoing drug-taking and relapse to drug-seeking across multiple drugs of abuse, although studies indicate a complex temporal relationship between exposure to the social stressor and elevation of drug intake, including temporary suppression of proximal drug-taking in the case of alcohol. An important line of future investigation should address the long-term impact of social stress history on drug self-administration, because existing data for alcohol suggest that protracted effects of defeat history may be more pronounced than the acute post-defeat effects that comprise the majority of existing data. Nonetheless, the comparability of social stress effects in rodents and humans affirms the use of social defeat as a paradigm for investigating putative pharmacotherapies developed to ameliorate the impact of social stress on drug consumption.

5. Pharmacological targets

Patients with comorbid PTSD and substance abuse often receive separate treatments for their disorders, rather than having the comorbid diagnosis addressed as a single illness with a common pathophysiology. Thus determining the efficacy of existing treatment options in models of stress/drug interactions may be useful for improving therapy options. In addition, exploring new options suggested by molecular targets with success in reducing stress-induced increases in drug self-administration in rodents has promise for providing better treatment options for individuals suffering from both PTSD and substance use disorders.

Neuropeptides that both positively and negatively regulate stress responses also modulate the negative emotional state generated by drug dependence (reviewed in Koob, 2008). One brain system that may underlie the interaction between stress and drug use is the extended amygdala, a neural circuit that includes the central nucleus of the amygdala, the bed nucleus of the stria terminalis and the shell of the nucleus accumbens (Alheid and Heimer, 1988). As the extended amygdala lies at the interface of the stress and drug reward systems, it is uniquely positioned to coordinate stress and drug responses. The amygdala has consistently been suggested as a brain region central to PTSD, as multiple fMRI studies have demonstrated elevated amygdala reactivity in PTSD patients (reviewed in Liberzon and Sripada, 2008). The extended amygdala is also rich in expression of several peptides, as well as their cognate receptors, involved in modulating stress responses. Anxiogenic neural signaling systems, including norepinephrine, corticotropin-releasing factor (CRF), dynorphin, vasopressin, and orexin (also known as hypocretin), increase stress-like behavior and relapse to drug-seeking in rodents, while neuropeptides that reduce anxiety-like behavior in rodents, such as serotonin, neuropeptide Y (NPY) and nociceptin, can inhibit stress-induced reinstatement. This section presents an overview of pharmacological data from rodent models of stress-induced drug seeking which suggests several new targets that deserve consideration as possible treatments for comorbid PTSD and substance use disorders.

5.1 Serotonin

The drugs most commonly prescribed to patients diagnosed with PTSD are the selective serotonin reuptake inhibitors (SSRIs), a class of drugs that block the serotonin transporter, thereby enhancing serotonergic signaling. A polymorphism in the serotonin transporter has been associated, in conjunction with trauma history, with elevated risk for developing PTSD (Xie et al., 2009) (but see also (Grabe et al., 2009)), supporting the focus on the serotonin system for PTSD medication. However, few investigations have explored the efficacy of SSRIs to reduce stress effects on drug self-administration in rodents. The existing data

suggest some ability for SSRIs to reduce stress-induced drug intake. Paroxetine treatment significantly reduced both anxiety-like behavior and alcohol intake in adult rats with a history of extended maternal separation (Huot et al., 2001), with 20-day paroxetine treatment prior to testing indicating good predictive validity for the amelioration of protracted effects of human childhood trauma by SSRIs. Fluoxetine was shown to decrease both maintenance operant alcohol self-administration and footshock-induced reinstatement of alcohol-seeking (Le et al., 1999). This inhibition of footshock-induced reinstatement was later confirmed with dexfenfluramine, a serotonin releaser and reuptake inhibitor, as well as the serotonin 3 receptor antagonists ondansetron and tropisetron, all of which are hypothesized to increase overall activity of the serotonin system (Le et al., 2006). It should be noted that Le and colleagues administered SSRIs acutely prior to the reinstatement sessions, a dosing regimen unlike that required for efficacy in humans. Regardless, these data suggest that the existing first treatment of choice for PTSD may also reduce stress-heightened drug intake or relapse.

5.2 Norepinephrine

Norepinephrine (noradrenaline), a neurotransmitter that binds to adrenergic receptors (ARs) to modulate physiologic processes involved in attention and arousal, has been implicated as one possible mediator of symptoms associated with PTSD (reviewed in Southwick et al., 1999). Dysregulation of the system has been observed in human PTSD sufferers, who show elevated norepinephrine levels in cerebrospinal fluid (CSF) (Geracioti et al., 2001; Geracioti et al., 2008), indicating enhanced activity of the central adrenergic system. The system presents an attractive target for the interaction between PTSD and drug abuse, as it may regulate elevated drug intake in dependent individuals and stress-induced reinstatement. Antagonism of the α1-AR by prazosin reduced heroin (Greenwell et al., 2009), cocaine (Wee et al., 2008), and alcohol (Walker et al., 2008) self-administration in rat models of dependence-heightened drug taking. Prazosin also attenuated the hypohedonic-like effects of nicotine withdrawal as determined by elevated ICSS thresholds (Bruijnzeel et al., 2010). Similar to α1-AR antagonists, inhibition of the β-AR reduced nicotine withdrawal symptoms, although its effects centered on the somatic rather than the affective aspects of withdrawal (Bruijnzeel et al., 2010). The β-AR antagonist propranolol also reduced dependence-heightened alcohol self-administration (Gilpin and Koob, 2010) as well as stress-induced cocaine (Mantsch et al., 2010) and cue-induced nicotine (Chiamulera et al., 2010) reinstatement in rats. Unlike the α1- and β-ARs, the α2-AR functionally inhibits adrenergic system activity. Thus, systemic administration of α2-AR agonists reduced somatic withdrawal signs for multiple drugs of abuse (Bruijnzeel et al., 2010; Riihioja et al., 1997; Tierney et al., 1988). α2-AR agonists also prevented stress-induced reinstatement of alcohol (Le et al., 2005), cocaine (Erb et al., 2000), heroin (Shaham et al., 2000), and nicotine (Zislis et al., 2007) self-administration. Because α2-AR agonists block stress-induced reinstatement, blockade of α2-ARs was hypothesized to mimic the effects of stressors on drug self-administration. As predicted, the α2-AR antagonist yohimbine, an anxiogenic-like compound, has been shown to substitute for stress exposure in the reinstatement of alcohol- (Le et al., 2005), psychostimulant- (Feltenstein and See, 2006; Shepard et al., 2004), and opiate-seeking (Banna et al., 2010). These results suggest inhibition of the norepinephrine system, via antagonism of α1- or β-ARs or agonism of α2-ARs, as a potential therapeutic target in individuals suffering from substance abuse secondary to stress disorders.

5.3 CRF

Among the stress-generating neuropeptide systems, the greatest wealth of evidence exists for regulation of drug-seeking by CRF, the neuropeptide responsible for initiating the canonical neuroendocrine stress response as well as behavioral responses to stressors.

Elevated CRF levels have been demonstrated in the CSF of PTSD patients (Bremner et al., 1997), supporting the proposal that altered central CRF levels may regulate the interaction between PTSD and drug abuse in humans. Involvement of extrahypothalamic CRF systems in stress-induced reinstatement of drug-seeking has been demonstrated for alcohol (Le et al., 2000), cocaine (Erb et al., 1998), heroin (Shaham et al., 1997), and nicotine (Zislis et al., 2007). Most data implicate the CRF_1 receptor in CRF modulation of elevated self-administration and reinstatement triggered by footshock stress (Bruijnzeel et al., 2009; Gehlert et al., 2007; Shaham et al., 1998) or yohimbine injection (Marinelli et al., 2007). Recently a CRF_1 antagonist has also been shown to inhibit social defeat stress-induced locomotor sensitization to and escalated "binge" operant self-administration of cocaine (Boyson et al., 2011). As CRF_1 antagonists also reduce drug-taking in substance-dependent animals (Koob, 2010), they present attractive targets for continued drug development to combat drug addiction and its interaction with stress.

5.4 KOR/dynorphin, vasopressin and orexin

Like CRF, the kappa opioid receptor (KOR) and its endogenous ligand, dynorphin, as well as vasopressin and orexin have all been shown to modulate stress-induced reinstatement. Multiple studies have demonstrated KOR antagonist inhibition of both footshock- and swim stress-induced reinstatement of cocaine- (Beardsley et al., 2005; Carey et al., 2007; Redila and Chavkin, 2008) and alcohol-seeking (Sperling et al., 2010). Fewer data exist for vasopressin and orexin, although human PTSD data showing upregulation of plasma vasopressin (de Kloet et al., 2008) and downregulation of plasma and CSF orexin-A (Strawn et al., 2010) support a role for these peptides in the neuroadaptations underlying the disorder. Studies in rodents suggest similar effects for inhibition of vasopressin and orexin as observed for norepinephrine, CRF and dynorphin. Antagonism of the vasopressin V1b receptor blocked stress-induced reinstatement of heroin-seeking (Zhou et al., 2008) and withdrawal-induced elevated alcohol self-administration in dependent rats (Edwards et al., 2008). Blockade of the orexin-A receptor inhibited yohimbine-induced reinstatement of alcohol-seeking (Richards et al., 2008), as well as stress-induced reinstatement of cocaine self-administration (Boutrel et al., 2005). Together, these data suggest that dynorphin, vasopressin and orexin, like CRF and norepinephrine, potentiate stress-induced reinstatement of drug-seeking. However, the efficacy of these systems in modulating protracted stress effects on drug self-administration remains to be determined.

5.5 Anxiolytic neuropeptide systems: NPY and nociceptin

Most extant data addressing the role of anxiolytic neuropeptide systems in regulating drug intake has focused on alcohol. Activation of the NPY system decreased alcohol intake in female rats following a deprivation period (Bertholomey et al., 2011; Gilpin et al., 2008; Gilpin et al., 2003), as well as blocking dependence-induced escalation of alcohol self-administration in male rats (Gilpin et al., 2011). NPY also reduced stress-induced reinstatement of alcohol-seeking in male rats (Cippitelli et al., 2010). Further research is required to determine NPY efficacy following a history of, rather than acute exposure to, stress. Data from human PTSD patients, who show reduced CSF NPY levels (Sah et al., 2009), support the proposed upregulation of NPY signaling as a means of treating PTSD and comorbid substance abuse. However, determination of the applicability of these findings to other drugs of abuse is vital, as NPY itself has been shown to elevate cocaine self-administration (Maric et al., 2009) and to reinstate heroin-seeking (Maric et al., 2008).

Like NPY, the bulk of nociceptin studies have focused on alcohol. Activation of the nociceptin receptor (NOP) blocked drug-induced reinstatement of alcohol CPP (Kuzmin et al., 2003) and stress- (Martin-Fardon et al., 2000) and cue-induced (Ciccocioppo et al., 2004) reinstatement of alcohol self-administration. Additionally, deprivation-induced

elevated alcohol self-administration was inhibited by NOP agonism and prolonged by NOP antagonism (Kuzmin et al., 2007), suggesting a role for nociceptin/NOP in dampening alcohol intake, although these effects may not be stress-specific. Applicability to other drugs of abuse is debatable, as NOP agonist treatment inhibited drug-primed reinstatement of morphine CPP (Shoblock et al., 2005), but was ineffective in blocking stress-induced reinstatement of cocaine-seeking (Martin-Fardon et al., 2000). Thus although potential promising targets for future treatments for alcohol use disorders, more investigation is required into the generality of therapeutic-like efficacy of activating anxiolytic neuropeptide systems.

5.6 Summary

Given the high prevalence of comorbidity between anxiety disorders and substance abuse (Grant et al., 2005) and the reduced efficacy of existing treatments in these comorbid patients as compared to those suffering only from substance use disorders (Brown et al., 1995; Brown and Wolfe, 1994), priority should be given to developing new therapies for the comorbid disorders. Systems involved in regulating stress responses show promise for medication development to treat drug problems in PTSD patients.

6. Conclusions

Comorbid stress and substance use disorders, often observed in patients with PTSD, present a major health care burden without sufficient effective treatment strategies. Existing rodent models demonstrate that a variety of stressors elevate the acute response to, intake of, and relapse to drugs of abuse in the wake of stress exposure, although additional efforts should be directed towards determining the protracted effects of traumatic stress on drug self-administration. As prototypic models of early life trauma and adult stressors, maternal separation, footshock, and social defeat may provide key tools for the development of further models and therapies to treat co-occurring PTSD and addiction.

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HIGHLIGHTS

- We review literature on traumatic stress effects on rodent drug self-administration.
- Early life stress and social and nonsocial stress in adulthood impact drug use.
- Stress exposure acutely elevates all phases of drug self-administration.
- Traumatic stress may also have long-term impact on drug taking and relapse.
- We discuss several therapeutic targets for post-traumatic and drug use disorders.

Figure 1.

Temporal modulation of stress effects on drug-seeking in rodents. Stress exposure acutely elevates behavioral responses to drugs of abuse and drug-seeking at all phases of drug self-administration. Post-stress increases in drug-seeking are usually short-lived, dissipating within 24h after cessation of the stressor. The effects of traumatic stress history on drug-seeking begin to emerge again after an interval, postulated to be on the order of days to several weeks depending on the nature and severity of the stressor. These distal stress history-dependent elevations in drug-seeking behavior may persist for weeks or even months, akin to the effects of post-traumatic stress on human drug-seeking.

Table 1

Selected protracted effects of adult psychological stressors on drug responsiveness and self-administration

Stressor	Drug	Effect	Reference
Chronic variable stress			
	Psychostimulants	Enhanced acute amphetamine reduction in ICSS thresholds	(Lin et al., 2002)
		Elevated acute locomotor response to cocaine	(Haile et al., 2001)
		Blocked low-dose amphetamine CPP	(Papp et al., 1991)
	Opiates	Elevated locomotor response to low -dose morphine	(Molina et al., 1994)
		Attenuated morphine CPP	(Valverde et al., 1997)
Footshock			
	Alcohol	Alcohol-preferring rat lines HAD and P escalate alcohol drinking 1–3 weeks after shock cessation	(Vengeliene et al., 2003)
		Increased alcohol preference 24h after completion of shock exposure	(Volpicelli and Ulm, 1990)
		Elevated alcohol intake beginning 1 week after shock exposure	(Casey, 1960)
Forced swim			
	Alcohol	Increased intake 3 weeks after cessation of stress	(Lowery et al., 2008)
	Psychostimulants	Enhanced cocaine CPP	(Kreibich et al., 2009)
Restraint			
	Alcohol	Increased moderate drinkers' intake and decreased high drinkers' intake during first 5 days post-stress	(Rockman et al., 1986)
		Transiently elevated preferring P rats' intake on the first day post-stress; prolonged elevation in non-preferring NP rats' intake from the third day post-stress	(Chester et al., 2004)
		Elevated alcohol intake over 3 weeks post-stress	(Nash and Maickel, 1985)
	Psychostimulants	Increased acute locomotor response but not sensitization to amphetamine	(Deroche et al., 1992)
	Opiates	Elevated acute locomotor response but not sensitization to morphine	(Deroche et al., 1992)
Tail pinch			
	Psychostimulants	Increased locomotor sensitization and acquisition of amphetamine self-administration	(Piazza et al., 1990)
Tail shock			
	Psychostimulants	No change in locomotor response to amphetamine	(Will et al., 2002)
	Opiates	Elevated acute locomotor response to morphine	(Will et al., 2002)
		Increased morphine CPP	(Will et al., 1998)

Table 2

Footshock delivery parameters used in cited studies

Intensity & Duration	Frequency	Subjects	Drug & References
0.2 mA, 0.5 sec	FT2min, 15 shocks, 10 days	adult & adolescent male & female mice	Alcohol: Chester et al. (2008)
0.2 mA, 0.2 sec	10 shocks	adult male rats	Cocaine: Sanchez and Sorg (2001)
0.6 mA, 0.1 sec	RR15, mean 50 shocks 25–35 days	adult male rats	Cocaine: Goeders and Guerin (1994)
0.23–0.42 mA, 0.5 sec	VI40sec, 15 min session	adult male mice	Alcohol: Matthews et al. (2008)
0.25 mA, 1 sec	10 shocks in 10 min	adult male rats	Cocaine: Ramsey and Van Ree (1993)
0.25, 0.5, 0.75 mA, 0.5 sec	VI40sec, 15 min session	adult male rats	Cocaine: Buffalari and See (2009)
0.5 mA, 0.1 sec	55–60s ITI, 5 shocks	adult male mice	Alcohol: Racz et al. (2003)
0.5 mA, 0.5 sec	VI40sec, 10 min session	adult male rats	Alcohol: Dayas et al. (2004), Liu and Weiss (2002), Liu and Weiss (2003); Cocaine: Erb et al. (1996); Heroin: Shaham and Stewart (1994), Shaham et al. (1996, 1998)
0.6 mA, 0.1 sec	VI74sec, 1 h, >35 days	adult male rats	Methamphetamine: Moffett and Goeders (2005)
0.6 mA, train of 3 × 0.1 sec, 1 sec apart	VI45sec, 5 min session	adult male rats	Cocaine: Mantsch and Katz (2007)
0.7 mA, max 0.8/8 sec[a]	FT1min, 2 h, 20 days	adult male rats	Alcohol: Cicero et al. (1968)
0.7 mA, max 3/15 sec[a]	FT1min, 30 min, 38days	adult male rats	Alcohol: Opsahl and Hatton (1972)
0.7 mA, 2.5 sec	1/h or 6/h, 14 days	adult male rats	Alcohol: Myers and Holman (1967)
0.8 mA, 0.5 sec	VI40sec, 5–20 min session	adult male rats or mice	Alcohol: Le et al. (1998, 2002)*rats*; Cocaine: Brown and Erb (2007) *rats*, Redila and Chav in (2008) *mice*
0.8 mA, 1 sec	VI33sec, 10 min, 5 days	adult male rats	Alcohol: Funk et al. (2004)
0.8 mA, 2 sec	FT1min, 1 h; 4 or 10 days	adult male rats	Alcohol: Fidler and LoLordo (1996), Volpicelli et al. (1986)
0.8 mA, 5–15 sec	5 min shock/10 min, 3 days	adult male rats	Alcohol: Vengeliene et al. (2003)
0.8 mA, up to 30 sec	VI60sec, 50 trials, 3 days	adult male rats	Alcohol: Volpicelli and Ulm (1990)
0.86 mA, 0.5 sec	VI40sec, 15 min	adult male rats	Cocaine: Ahmed and Koob (1997)
1 mA, 0.5 sec	VI40sec, 15 min	adult male rats	Heroin: Ahmed et al. (2000)
1 mA, 1 sec	VI30sec, 15 min	adult & adolescent male & female rats	Alcohol: Brunell and Spear (2005)
1 mA, 2 sec	FT1min, 1 h, 5 days	adult male & female rats	Alcohol: Caplan and Puglisi (1986)
1 mA, 5 sec	FT1min, 1 h	adult male rats	Alcohol: Volpicelli et al. (1990)
1.5 mA, 1 sec	12 min/h for 24 h, 15 days	adult male rats	Alcohol: Mills et al. (1977) Alcohol: Myers and Holman (1967)
2.5 mA, up to 5 sec	180/day, 3 days	adult male rats	Cocaine: MacLennan and Maier (1983)
35 V, 1.5 sec	VI11.3min for 16 days	adult male rats	Alcohol: Casey (1960)
40 V, 1 sec	15 shocks in 15 min	adult male mice	Morphine: Kuzmin et al. (1996)

[a]Rats could terminate shock train by lever pressing, trains involved 0.2 sec shock on, 2 sec shock off for 8 or 15 sec total if shock not terminated by lever press.

FT, fixed time between shock presentations

RR, random ratio indicating average number of lever presses resulting in shock delivery

VI, variable interval between shock presentations, with time reported as mean inter-shock interval