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Social defeat stress and escalation of cocaine and alcohol consumption: Focus on CRF

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ABSTRACT

Both the ostensibly aversive effects of unpredictable episodes of social stress and the intensely rewarding effects of drugs of abuse activate the mesocorticolimbic dopamine systems. Significant neuroadaptations in interacting stress and reward neurocircuitry may underlie the striking connection between stress and substance use disorders. In rodent models, recurring intermittent exposure to social defeat stress appears to produce a distinct profile of neuroadaptations that translates most readily to the repercussions of social stress in humans. In the present review, preclinical rodent models of social defeat stress and subsequent alcohol, cocaine or opioid consumption are discussed with regard to: (1) the temporal pattern of social defeat stress, (2) male and female protocols of social stress-escalated drug consumption, and (3) the neuroplastic effects of social stress, which may contribute to escalated drug-taking. Neuroadaptations in corticotropin-releasing factor (CRF) and CRF modulation of monoamines in the ventral tegmental area and the bed nucleus of the stria terminalis are highlighted as potential mechanisms underlying stress-escalated drug consumption. However, the specific mechanisms that drive CRF-mediated increases in dopamine require additional investigation as do the stress-induced neuroadaptations that may contribute to the development of compulsive patterns of drug-taking.

1. Introduction

The neural mechanisms for coping with social stress and for escalated drug use interact in an intricate manner (Sinha, 2001). How the ostensibly aversive effects of unpredictable episodes of social stress and the intensely rewarding effects of self-administered cocaine infusions concurrently activate the mesocorticolimbic dopamine system remains unresolved. Moreover, this apparent paradox is accentuated by the persistent escalation of cocaine self-administration binges in socially defeated animals that are characterized by elevated dopamine tone (Holly and Miczek, 2016).

Psychomotor stimulants such as amphetamines and cocaine are self-administered at escalated levels after intermittent exposure to various stressors, whereas the stress parameters are much more limited for escalating alcohol and opiate intake (Ahmed et al., 2018; Becker et al., 2011). This review describes the different kinds of social defeat stress and focuses on their cross-species generality and ready translation from experimental animal models to stress-related alcohol and substance use disorders in humans.

Social stress is bi-directional in nature. The ascending limb of this inverted U-shaped curve delineates the energizing, activating effects of mild to moderate stress while the descending limb signifies the potentially debilitating, impairing effects of severe or chronic stress (Sapolsky, 2015). In this review, we discuss how a history of mild, moderate or more severe social defeat stress exposure can ultimately increase or decrease voluntary drug-taking in preclinical animal models.

The neuropeptide, corticotropin-releasing factor (CRF or CRH; encoded by the *CRH* gene), exerts a salient role in the interacting neural networks for social stress and for drug abuse initiation, escalation and relapse (Bernardi et al., 2017; Sarnyai et al., 2001). Most types of social stress are characterized by hypothalamic CRF activating the hypothalamic pituitary adrenal (HPA) axis in the laboratory and in the field (Covington and Miczek, 2005; Fuchs and Flügge, 2002; Norman et al., 2015; Sapolsky 1990, 1992; Sgoifo et al., 1998). In addition, considerable evidence points to the significance of ***extrahypothalamic*** CRF as a modulator of canonical monoamine neurotransmitters (Kelly and Fudge, 2018). We focus on extrahypothalamic CRF signaling due to its

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critical role in modulating motivation, especially in the context of drug seeking and consumption (Holly and Miczek, 2016; Koob and Volkow, 2010; Wise, 2004).

2. Clinical overview: social stress as a risk factor for drug use

2.1. Alcohol

For some individuals, moderate alcohol consumption increases the desire to engage in prosocial behaviors and renders these social interactions more enjoyable; likewise, social settings can increase total alcohol intake as well as the positive subjective effects of alcohol (de Wit and Sayette, 2018; Van Hedger et al., 2017). Under these conditions, drinking tends to be context-dependent, and cessation of alcohol consumption generally coincides with removal from the social context. While drinking to enhance mood is generally not associated with later, problematic drug use, those who consume alcohol in negative social contexts to reduce social anxiety and stress may be more likely to later meet the Diagnostic and Statistical Manual (DSM-V; American Psychiatric Association, 2013) criteria for an alcohol use disorder (AUD; Cooper et al., 1992b; Sinha, 2001). And in more extreme cases, exposure to moderate or severe psychosocial stressors can further increase the likelihood of developing a sustained pattern of uncontrollable drinking or the probability of future relapse, particularly in those who drink as a coping mechanism (Adinoff et al., 2017; Brown et al. 1990, 1995; Koob and Kreek, 2007). This review will evaluate the characteristics of social stressors that may increase the probability of escalated drinking or drug-taking.

There is substantial evidence pointing to stress exposure and stress responding as predictors of alcohol use in humans (Brown et al. 1990, 1995; Gilpin and Weiner, 2017; Sinha 2001, 2008, 2009; Stewart, 1996; Uhart et al., 2006; Uhart and Wand, 2009). Most clinical experimental studies on social stress and drug-taking use the Trier Social Stress Test (TSST), which can reliably increase circulating cortisol levels and heart rate in response to social examination and performance stress (Allen et al., 2017; Kirschbaum et al., 1993). When asked to complete the TSST, craving and responding for alcohol as well as total alcohol intake increase in participants with an alcohol use disorder compared to healthy controls, suggesting that alcohol-dependent individuals may be more likely to cope with negative affective states by drinking (McCaul et al., 2018; Thomas et al., 2011; Van Hedger et al., 2017). In addition, non-abstaining, alcohol-dependent participants exhibit an augmented stress response compared to abstaining patients or healthy controls (Starcke et al., 2013), indicating that heightened stress reactivity in heavy-drinking individuals may intensify alcohol craving in response to mild stressors.

2.2. Cocaine

Stressful life events can promote excessive cocaine use and increase the probability of relapse in dependent individuals (Sinha, 2001; Wallace, 1989). Cocaine-dependent adults who report higher levels of perceived stress and anxiety appear to take cocaine for more years than those who report less stress and anxiety (Karlsgodt et al., 2003). When asked to imagine and recount a recent stressful life event during a stress imagery task, healthy participants show a characteristic increase in salivary cortisol concentrations which then decline during a subsequent recovery period. However, in cocaine abusers, cortisol levels continue to rise even during the recovery period and these individuals also report increased drug craving as a consequence of performing this task (Sinha et al., 1999, but Harris et al., 2005). During a similar, drug cue imagery procedure, participants recall a recent circumstance that involved drug-related cues and triggered cocaine-taking. As with stress imagery, visualizing drug cues also increases salivary cortisol and drug craving; however, only craving in response to stress imagery, but not drug cue imagery, strongly predicts imminent relapse to cocaine. Likewise, stress-induced increases in cortisol are predictive of the amount of cocaine taken during the relapse (Sinha et al. 2000, 2006; Waldrop et al., 2010). Unlike drug cue imagery, craving in response to direct contact with drug paraphernalia is predictive of relapse in dependent individuals. And, like stress imagery, direct stimulation of the HPA axis with intravenous CRF treatment also produces predictive subjective effects (Back et al., 2010), suggesting that individual differences in HPA axis reactivity and craving in response to stress and drug cues may determine the trajectory of cocaine abuse and treatment outcome.

In an evaluation of recently abstaining cocaine-dependent patients, both stress and drug cue imagery increased negative emotions including feelings of sadness, anger, fear and anxiety. Compared to healthy controls, patients also reported more severe craving for drugs and alcohol in response to stress or drug cue imagery (Fox et al., 2008). For cocaine-dependent outpatients, the effects of stress exposure are potentiated by drug-related cues, and individuals who frequently encounter both environmental stimuli are at the greatest risk of experiencing intense urges to take cocaine (Preston et al., 2018). A similar study using fMRI reported a decrease in anterior cingulate and an increase in dorsal striatal activity during stress imagery in patients compared to healthy individuals, suggesting reduced regulation of brain areas that may exert control over subcortical, reward- and craving-associated regions (Sinha et al., 2005). Together, these findings indicate that stress and drug-related cues can intensify the desire to take cocaine, thereby increasing the risk of relapse in abstinent, cocaine-dependent individuals. In addition, stress-induced neuroadaptations may result in a dysregulation of striatal activity and increased drug abuse risk. Using this information in conjunction with potentially predictive imaging techniques and neuroendocrine measures of HPA axis reactivity, specific therapies could be designed to specifically treat stress-associated relapse to cocaine abuse (Milivojevic and Sinha, 2018; Sinha and Li, 2007).

2.3. Opioids

Lifetime traumatic experiences including childhood maltreatment, assault and domestic violence increase the risk of developing an opioid addiction (Lawson et al., 2013), and opioid abuse may be perpetuated by continued exposure to traumatic events, particularly in the form of physical violence (Cottler et al., 1992). Treatment-seeking, opioid-dependent patients describe greater levels of perceived stress than healthy controls (Hyman et al., 2009). The intensity and frequency of these stressful experiences is associated with more intense drug craving (Kowalczyk et al., 2015; Preston et al., 2017; Preston and Epstein, 2011), while the number and magnitude of life crises increases the likelihood of relapse (Kosten et al., 1986; Krueger, 1981). Greater perceived stress in opioid addicts may result from an amplified sensitivity to stressful stimuli due to a history of traumatic life events; in turn, this may render some individuals more likely to develop an opioid addiction and more vulnerable to relapse (Kosten et al., 1986; McCabe et al., 2016; Sinha 2001, 2007).

In a laboratory setting, opioid-dependent patients report severe drug craving, anxiety and fear during stress or drug cue imagery tasks, whereas only stress imagery escalates heart rate, systolic blood pressure, and self-reported feelings of anger and sadness (Hyman et al., 2007; Sinha et al., 2007). Likewise, during the TSST, opioid-dependent individuals report more negative, subjective effects of social stress compared to healthy controls (Back et al., 2015). Outside of the laboratory, however, stress and drug cues are often experienced in tandem. Faced with concurrent stressful situations and drug-related paraphernalia, heroin-dependent outpatients report an increase in the severity of craving (Preston et al., 2018). In sum, these findings point to a combined role of stressors and drug-related cues as environmental risk factors that may increase the probability of relapse to opioid abuse.

Regarding physiological measures of stress reactivity, heroin-dependent patients exhibit higher circulating cortisol and ACTH concentrations compared to healthy individuals, and an acute dose of

heroin can normalize these measures (Schmidt et al., 2014; Walter et al., 2013). Correspondingly, fMRI reveals an augmented left amygdala response to fearful faces in patients; this can also be normalized with acutely administered heroin (Schmidt et al., 2014). Peripheral measures of stress reactivity may correlate with relapse probability (Jaremko et al., 2015). However, a single systemic dose of cortisol does not increase the desire to take heroin (Walter et al., 2015). Deficits in the neural mechanisms that typically provide negative feedback to the HPA axis may ultimately produce both cravings and elevated cortisol levels in heroin users. Together, environmental risk factors like stress and drug-related cues and individual differences in stress reactivity are likely to interact and influence the likelihood of opioid abuse and relapse.

3. Animal models of social stress and pathological patterns of drug-taking

Because clinical experiments are bound by ethical constraints on the type and duration of laboratory stressors, studies aiming to clarify the effects of ***repeated*** or ***continuous*** social stress exposure predominantly employ rodent models. This review focuses on (1) preclinical models of social stress-heightened alcohol drinking and drug-taking, (2) the possible neurobiological mechanisms underlying interactions between social stress and drugs of abuse, and (3) avenues of future research and promising therapeutic targets for the treatment of drug or alcohol use disorders in individuals with a history of social stress exposure.

3.1. Temporal patterns of social defeat stress and drug-taking

3.1.1. Alcohol

A key feature of experimental protocols that study the link between social stress and escalated alcohol consumption is the timing of the stress episodes. While it is apparent that ***repeated*** episodes of social defeat stress are required to produce a pattern of stress-escalated alcohol consumption (Croft et al., 2005), the temporal pattern of these stress episodes differs vastly between protocols, ranging from intermittent to chronic.

Ten consecutive days of intermittent social defeat stress can produce significant, persistent increases in voluntary alcohol consumption in both C57BL/6J (Fig. 1; Albrechet-Souza et al., 2017; Hwa et al., 2016a; Newman et al., 2018) and outbred, Swiss-derived mice (Norman et al., 2015). During ***intermittent*** resident-intruder confrontations, an aggressive, physical encounter is terminated after a fixed duration or number of attack bites (e.g., 5 min or 30 bites). Between daily stress episodes, experimental mice are singly housed, which is the primary feature that distinguishes intermittent from continuous social defeat stress protocols.

Continuous social defeat stress models in rodents often employ 5–10 min daily resident-intruder confrontations. In the interval between aggressive encounters, defeated animals are housed adjacent to an aggressor, but protected by a perforated partition (Golden et al., 2011; Kudryavtseva et al., 1991). While the physical attack periods remain ***intermittent***, "threatening" housing conditions are ***continuous***. Experimental mice are attacked by a different aggressive resident every day, and subsequently housed next to that aggressor until the following defeat episode. Models of continuous social defeat stress in C57BL/6J (B6) female (Newman et al. in prep) and male mice (Kudryavtseva et al., 2006; Nelson et al., 2018) can lead to persistently escalated alcohol consumption.

In ***chronic*** subordinate colony (CSC) stress models, several submissive male mice are housed in the territory of an aggressive resident over the course of days to weeks without the protection of a perforated partition or cage. Following CSC stress, submissive mice voluntarily consume more alcohol compared to either singly-housed controls (Bahi, 2013; Peters et al., 2013) or dominant males (Hilakivi-Clarke and Lister, 1992). Similar findings are reported using CSC protocols in rats (Blanchard et al. 1987, 1992; Ellison, 1987), in evaluations of social dominance among prairie voles (Anacker et al., 2014), and in socially housed squirrel monkeys (McKenzie-Quirk and Miczek, 2008); likewise, social dominance appears to have a protective effect against escalated alcohol intake in cynomolgus monkeys (Helms et al., 2012; Jimenez and Grant, 2017). In rats, pre-stress alcohol intake does not correlate with later hierarchical standing or drinking following CSC stress, indicating that elevated drinking likely results from subordination stress rather than individual differences in alcohol preference (Blanchard et al., 1992; Hilakivi-Clarke and Lister, 1992, but Wolffgramm and Heyne, 1991). While the CSC protocol can reveal stress-escalated alcohol drinking in submissive mice and rats, it is difficult to ensure that defeated animals are stressed equally, and therefore, these models demand large group sizes. In addition, CSC stress can result in severe injuries inflicted by dominant animals onto submissive animals, making it impossible to distinguish between changes in drinking due to psychosocial stress exposure or due to pain associated with injury or infection. In light of these limitations, the neuroadaptations associated

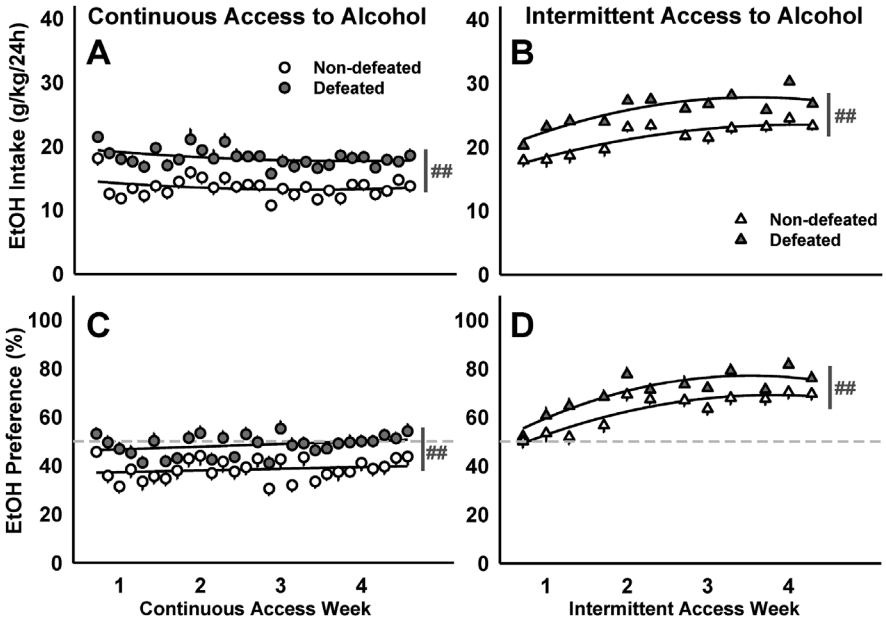

Fig. 1. Socially defeated and non-defeated C57BL/6J males received 20% EtOH and water for 4 weeks. Daily mean ± SEM intake (g/kg/24 h) for mice with (A) continuous access to alcohol or (B) intermittent access to alcohol. The amount of alcohol consumed as a percentage of the total daily fluid intake (EtOH Preference) is depicted as daily mean ± SEM for mice with (C) continuous or (D) intermittent access to alcohol. Best-fit curves are in black. *##p* < 0.01 non-defeated vs. defeated. Dashed lines mark the preference cutoff: values > 50% indicate a preference for alcohol over water, while values < 50% indicate a preference for water over alcohol (adapted from Newman et al., 2018).

with social defeat stress and escalated drug-taking may be better studied in mice or rats with a history of continuous or repeated intermittent social defeat stress rather than CSC stress.

When animals are socially defeated and given alcohol concurrently or provided alcohol access immediately following a defeat episode, mice (Norman et al., 2015) and rats (Van Erp et al., 2001) often consume less alcohol than their non-defeated counterparts. Rats will similarly suppress their operant responding for alcohol when self-administration sessions are conducted soon after the social defeat episode (Funk et al., 2005; Van Erp and Miczek, 2001). Elevated drinking in socially defeated animals develops days or weeks ***following*** the final social defeat exposure, but not during or soon after the stress experience (Caldwell and Riccio, 2010; Croft et al., 2005; Lopez et al., 2016; Noori et al., 2014; Norman et al., 2015; Sillaber et al., 2002), suggesting that long-lasting neuroadaptations arise as a consequence of repeated episodes of social defeat stress. In addition, sympathetic activation during the stress exposure may initially suppress drug-taking, making the recovery from intense autonomic activity necessary for escalated drinking or self-administration to become apparent. In terms of the temporal pattern of social stress exposure, the duration and frequency of defeat stress episodes and the post-defeat interval prior to the onset of alcohol access are critical variables that require significant consideration.

3.1.2. Cocaine

In the laboratory, both rat and mouse models of intravenous cocaine self-administration reveal a relationship between social stress exposure and the acceleration towards an addiction-like phenotype that parallels clinical observations. Social stress can accelerate the acquisition of cocaine-taking (Tidey and Miczek, 1997; Arena et al. in prep), promote escalated and dysregulated patterns of drug consumption (Covington and Miczek, 2001; Han et al., 2015), and increase drug-seeking behavior after a drug-free period (Holly et al., 2016; Manvich et al., 2016).

Brief exposure to acute social defeat stress enhances the conditioned effects of psychostimulants, which may in turn promote the acquisition of self-administration behavior. Compared to non-defeated control animals, both mice and rats that are socially defeated immediately before receiving an injection of cocaine subsequently develop a greater preference for the drug-paired environment during conditioned place preference (CPP) testing (McLaughlin et al., 2006; Montagud-Romero et al., 2015; Tovar-Diaz et al., 2018). Likewise, exposure to social defeat stress over five consecutive days can double the rate of cocaine self-administration acquisition (Fig. 2A; Tidey and Miczek, 1997), and rats that receive access to cocaine within 24 h of a stress episode show transiently elevated rates of self-administration (Fig. 2B; Miczek and Mutschler, 1996; Tidey and Miczek, 1997). However, these effects are often absent in studies that examine the more ***protracted*** effects of social defeat stress on cocaine self-administration (Fig. 2D; Boyson et al., 2011; Covington and Miczek, 2001; Holly et al., 2016; Kabbaj et al., 2001; but Haney et al., 1995), emphasizing the importance of the duration between stress and the onset of cocaine availability.

Just as social stress can potently exacerbate drug-craving in people who are exposed to cocaine-associated cues (Preston et al., 2018; Sinha et al., 1999), acute exposure to social stress can reinstate a previously extinguished preference for drug-paired stimuli in a CPP protocol (Bruchas et al., 2011; Ribeiro Do Couto et al., 2009). However, modeling social stress-mediated reinstatement of operant behavior has proven challenging. Acute exposure to defeat fails to stimulate, and often suppresses conditioned responding on a drug-associated operandum in rodent models of both alcohol and cocaine self-administration (Funk et al., 2005; Manvich et al., 2016). The effects of stress on behavioral arousal adhere to an inverted U-shaped function, and social defeat may represent an especially salient stressor that approaches the descending limb of this curve, possibly resulting in the non-specific suppression of operant behaviors (McEwen et al., 2015; Sapolsky, 2015). Indeed, submissive rats escalate their rates of responding for cocaine immediately after a social threat protocol that prevents physical attack by using a protective barrier to shield the submissive rat from the dominant aggressor (Fig. 2B; Miczek and Mutschler, 1996). While this protocol limits physical injury, the submissive rat is still subjected to threatening auditory, olfactory and visual stimuli generated by the dominant resident. Similarly, re-exposure to stress-associated odor cues in the context of drug self-administration can reinstate previously extinguished cocaine-seeking behavior in rats (Fig. 2C; Manvich et al., 2016).

Intermittent exposure to social defeat can persistently increase and dysregulate typical patterns of cocaine self-administration. Brief, episodic social defeat stress tends to ***enhance*** measures of drug self-administration. Across a range of doses, defeat-experienced mice show a robust upward-shift in their rate of cocaine self-administration, indicating a persistent change in the drug's reinforcing effects (Fig. 2E; Han et al., 2015; Arena et al. in prep). In rats, episodic social defeat stress can increase progressive ratio breakpoints (Burke and Miczek, 2015; Covington and Miczek 2001, 2005; Quadros and Miczek, 2009) though this effect is not always evident (Boyson et al. 2011, 2014; Cruz et al., 2011; Miczek et al., 2011; Yap and Miczek, 2007).

Intermittent social defeat stress during adolescence or adulthood consistently intensifies binge-like cocaine consumption during prolonged periods of unlimited access to drug (24–48 h; i.e., the “binge” protocol). During these binges, both male and female rats with a history of episodic social defeat stress often accumulate twice as much cocaine as non-stressed controls (Fig. 2F; Boyson et al., 2011; Boyson et al., 2014; Burke et al., 2016; Burke and Miczek, 2015; Covington et al., 2005; Covington et al., 2008; Covington and Miczek, 2001; Covington and Miczek, 2005; Cruz et al., 2011; Holly et al., 2012; Leonard et al., 2017; Quadros and Miczek, 2009; Yap et al., 2015).

In contrast, under limited access conditions or during the early hours of the binge, many measures of cocaine self-administration are not affected by a history of social defeat stress. For instance, self-administration by defeated and control rats is indistinguishable during the early hours of access, and these animals show precise regulation of drug intake, even in the face of unpredictable changes in unit dose delivery (Covington et al., 2008; Quadros and Miczek, 2009). Likewise, stress exposure does not persistently alter how defeated animals value cocaine under limited access conditions (Leonard et al., 2017). These findings likely reflect a more nuanced disruption in the ***pattern*** of cocaine-taking engendered by repeated exposures to social defeat stress. Stress experience appears to disrupt the mechanisms that control the maintenance or termination of cocaine self-administration bouts, resulting in ***prolonged*** binges that often persist beyond 24 h. This binge-like phenotype may reflect blunted inhibitory control over continued drug-maintained behavior or deficits in the typical circadian patterns that regulate drug-taking (Covington et al., 2008; Fitch and Roberts, 1993).

In contrast with intermittent social defeat stress, ***prolonged*** exposure to social defeat in a continuous stress model can ***suppress*** cocaine self-administration in male and female rats (Miczek et al., 2011; Shimamoto et al., 2015). Rats obtain significantly fewer drug infusions under control of a progressive ratio schedule of reinforcement and accumulate less cocaine during a binge. Continuously defeated animals also show a lower saccharin preference compared to non-defeated rats, suggesting that intense, prolonged social stress may suppress a range of reward-related behaviors.

Social adversity can increase the likelihood of relapse and a history of social subordination can engender latent vulnerability to re-engage in drug-seeking behaviors. When historically defeated rats are exposed to a drug-associated environment fifteen days into forced abstinence, they begin responding on a formerly cocaine-paired operandum (Fig. 2F; Holly et al., 2016). In this case, sensitivity to the appetitive effects of drug-associated cues lasts more than a month after the final stress exposure. As such, cumulative prior stress experiences may magnify drug craving during periods of abstinence. This may pose a considerable obstacle for individuals to maintain sobriety, even in the

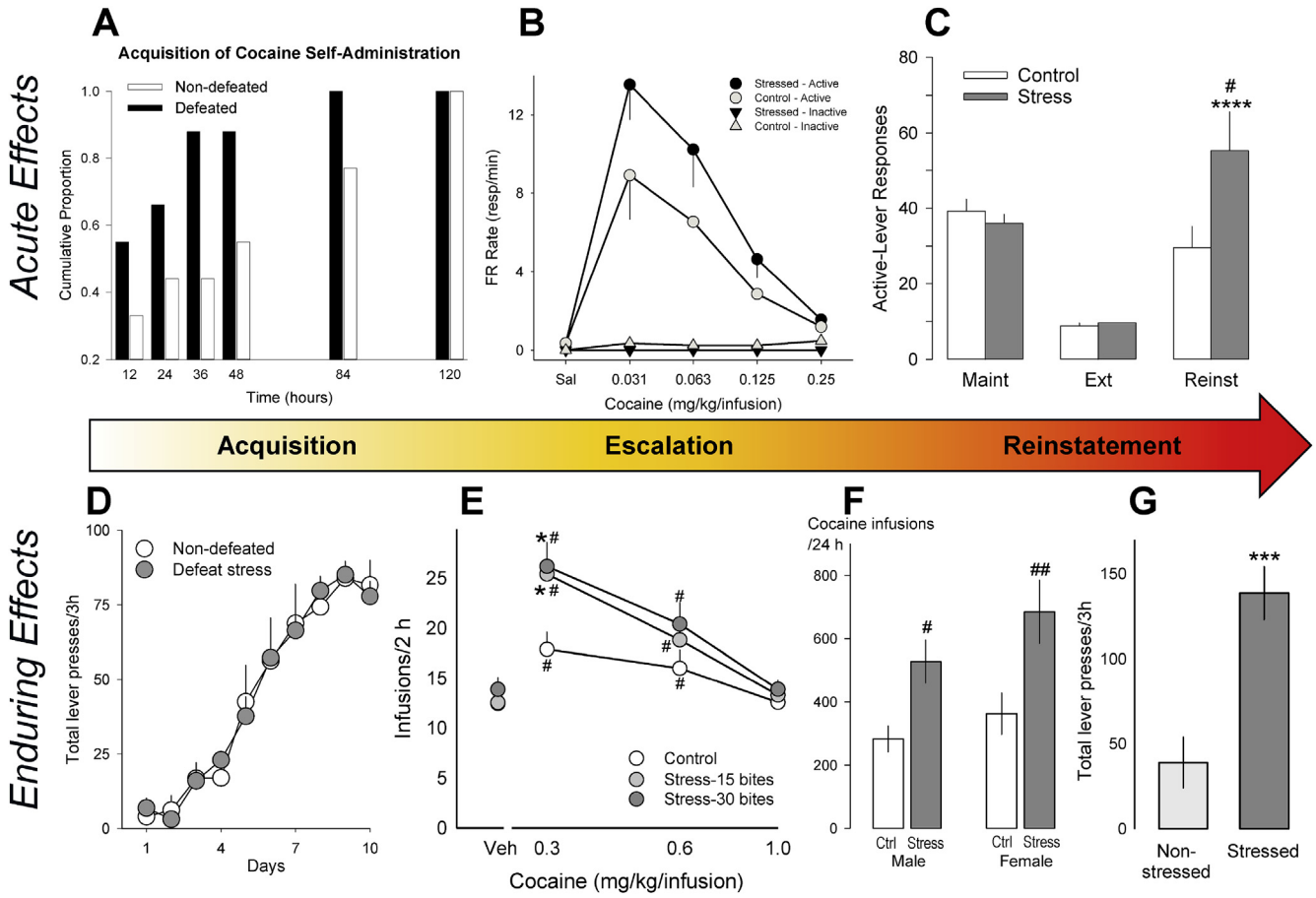

Fig. 2. The acute (A–C) and enduring (D–G) effects of social defeat stress on cocaine self-administration across phases of 'the addiction cycle'. A cumulative histogram (A) shows increased rates of acquisition of cocaine self-administration (0.25 mg/kg/infusion; FR1) for rats 24 h after defeat (black bars) compared to non-defeated rats (white bars); data are divided into 12 h bins of total drug access (adapted from Tidey and Miczek, 1997). (B) The dose-effect function for cocaine on rate of responding (resp/min) maintained by an FR5 schedule; determined by three sessions per dose, and shown as mean ± SEM. Rats exposed to social threat from an aggressive resident for 60 min immediately prior to each session (black circles) show elevated rates of responding for lower doses in comparison to non-stressed controls (white circles). Triangles depict the response rates on an inactive lever (adapted from Miczek and Mutschler, 1996). (C) Re-exposure to cues predictive of impending social defeat produces reinstatement of cocaine seeking; shown are the active-lever responses during the maintenance phase of self-administration ("Maint"), extinction ("Ext"), and reinstatement ("Reinst") following defeat-cue re-exposure (grey bars) or a non-stressful control condition (white bars). Data represent the mean ± SEM number of responses during the final three days of self-administration prior to the onset of stress sessions ("Maint"), the final three days of extinction ("Ext"), and a single reinstatement test session ("Reinst"). $^{****}p < 0.0001$ compared to extinction; $\#p < 0.05$ compared to the control group (adapted from Manvich et al., 2016). (D) No differences in the acquisition of cocaine self-administration (0.75 mg/kg/infusion) one week after intermittent social defeat (grey circles) or handling (white circles), across ten days of training (adapted from Holly et al., 2016). (E) The dose-effect function for cocaine intake is elevated in mice previously exposed to intermittent social defeat prior to self-administration (grey circles), relative to handled controls (white circles). Individual data were averaged over two sessions; $\#p < 0.05$, $\#\#p < 0.01$ compared to the control group (adapted from Han et al., 2015). (F) Total number of infusions during an unlimited access cocaine "binge" (0.3 mg/kg/infusion, FR1) are enhanced by exposure to intermittent social defeat stress (grey bars) prior to self-administration, compared to handled controls (white bars), in male and female rats. "Binge" terminated after 120 min without a cocaine infusion. $\#p < 0.05$, $\#\#p < 0.01$ compared to the control group (adapted from Holly et al., 2012). (G) Upon return to the cocaine self-administration chamber after days of forced abstinence, defeated rats (dark grey bar) pressed the previously cocaine-paired lever significantly more than non-stressed animals (light grey bar) over a 3 h session. $^{***}p < 0.001$ compared to the control group (adapted from Holly et al., 2016). All data are expressed as mean ± SEM, with the exception of (A).

absence of ongoing adversity.

3.1.3. Opioids

Aggressive encounters actively engage and modify endogenous opioid systems in rodents (Chaijale et al., 2013; McLaughlin et al., 2006; Miczek et al., 2008; Nikulina et al., 2005). However, a definitive link between social stress and opioid consumption has yet to be firmly established in preclinical models. Limited evidence in rodent preparations suggests that social defeat stress may transiently enhance opioid-dependent behavior, similar to psychostimulants, though the substrates underlying opioid reinforcement are quite distinct from those of psychostimulants or alcohol (Badiani et al., 2011).

Consistent with the observation that social stress can enhance drug craving in opioid-dependent individuals, acute social stress exposure reinstates morphine-induced CPP, which was previously extinguished (Ribeiro Do Couto et al., 2006). These findings parallel the effects of other stressors (e.g., footshock, tail-pinch), although it has been argued that physical stress modalities may, in part, engage endogenous opioid systems in response to minor injury, producing an increase in subsequent opioid-seeking or intake. A comparison between the effects of social defeat stress and the effects of a non-contact witness stress on morphine intake indicates that social threat may be sufficient to enhance the reinforcing effects of morphine, even in the absence of physical defeat (Cooper et al., 2017). Yet, despite enduring changes in gene expression and neural activity, morphine preference is no longer apparent two weeks after stress exposure. Similarly, intermittent exposure to social defeat does not engender lasting effects on binge-like heroin self-administration (Cruz et al., 2011). Together, these findings suggest

that ***ongoing*** adversity may significantly increase the likelihood of opioid use.

3.2. Male vs. female social stress and drug-taking

3.2.1. Alcohol

Alcohol use disorders are diagnosed more often in men than in women, possibly due to sex differences in stress reactivity or differences in the mechanisms used by men and women to cope with stressful life events (Cooper et al., 1992a; Greenfield et al., 2010; Nolen-Hoeksema, 2004). However, this gender gap is gradually diminishing (Greenfield et al., 2010; Grucza et al., 2008; Keyes et al., 2010; Wagner and Anthony, 2007) particularly with respect to stress-associated AUDs (Slopen et al., 2011). Some studies even report that women are at a greater risk of developing an AUD after experiencing repeated moderate or severe life stressors than men (Boden et al., 2014; Sannibale and Hall, 2011) and that women are more likely to relapse to heavy drinking in response to interpersonal conflict or unpleasant emotional states (Annis and Graham, 1995). With a significant subset of men and women suffering from stress-related AUDs, it is imperative to develop preclinical models to study the potentially dimorphic mechanisms underlying male and female social stress-escalated alcohol drinking (Becker and Koob, 2016).

In preclinical models of male social defeat stress, B6 or Swiss-derived outbred male mice exposed to repeated attacks from a dominant male resident later consume significantly more alcohol than non-defeated controls (Fig. 1; Albrechet-Souza et al., 2017; Hwa et al., 2016a; Karlsson et al., 2017; Kudryavtseva et al., 2006; Kudryavtseva et al., 1991; Nelson et al., 2018; Newman et al., 2018; Norman et al., 2015). Recently, we developed a model of social stress that promotes inter-female aggression to evaluate the effects of social defeat stress on alcohol consumption in female B6 mice (Newman et al. in prep). Using this protocol, nearly all resident CFW females will rapidly attack a novel B6 intruder female. Unlike other models of female social defeat stress that rely on either aggression from a lactating female conspecific (Brain and Haug 1992; Hashikawa et al., 2017; Holly et al., 2012; Jacobson-Pick et al., 2013; Shimamoto et al. 2011, 2015) or invasive experimental manipulations used to elicit pathological male aggression toward females (Harris et al., 2018; Takahashi et al., 2017), the present social defeat stress model takes an ethological approach by relying on characteristic female-directed female aggression. At present, there is no published model that evaluates the consequences of species-typical physical aggression in male and female mice using identical experimental conditions. Considering the notable differences in male and female patterns of aggressive behavior, employing sex-dependent social defeat stress models may be the ideal experimental approach to characterizing translational phenotypes in defeated animals.

Like B6 males that are intermittently defeated, continuously defeated B6 females consistently consume more 20% EtOH (w/v) than controls, and importantly, continuous social defeat stress does not permanently disrupt estrous cycling, suggesting that escalated drinking is not linked to defeat-induced acyclicity. This preclinical mouse model may be instructive in clarifying the biological mechanisms that contribute to the higher rate of co-occurring mood and substance use disorders in women than in men (Conway et al., 2006) and in screening potential pharmacotherapies for sex-dependent effects.

3.2.2. Cocaine

As with AUDs, more male cocaine-users are likely to meet the DSM-V diagnostic criteria for a substance use disorder (SUD) than women though this gender gap is gradually narrowing (Substance Abuse and Mental Health Services Administration, 2013). Compared to men, women are more likely to rapidly escalate to cocaine dependence (Cotto et al., 2010; McCance-Katz et al., 1999), to use cocaine more frequently (Chen and Kandel, 2002), and to relapse to cocaine use (Anker and Carroll, 2011; Becker and Hu, 2008; Becker and Koob, 2016; Ignjatova and Raleva, 2009). Clinical studies report greater subjective feelings of wellbeing in response to smoked cocaine in women, particularly during the follicular phase of the menstrual cycle when the ratio of estradiol to progesterone is high (Evans et al., 2002; Evans and Foltin, 2006; Sofuoglu et al., 1999). In the context of stress, cocaine-dependent females are often more sensitive to stress cues and imagery than healthy women or dependent men, which may increase relapse probability in these individuals (Back et al., 2005; Fox et al. 2006, 2008; Li et al., 2005; Potenza et al., 2012; Waldrop et al., 2010). Using translational preclinical models, we can investigate how interactions between long-lasting social stress effects and circulating female sex hormones may accelerate the trajectory of cocaine abuse in females compared to males (Lynch and Carroll, 1999; Roth et al., 2004).

Numerous studies illustrate that social defeat stress in male mice and rats can increase measures of cocaine self-administration. In B6 mice, submissive males that are exposed to 15–30 attack bites per day for ten consecutive days escalate their intravenous cocaine self-administration during 2 h sessions and show a heightened accumbal dopamine response to a challenge with a moderate dose of *d*-amphetamine relative to non-defeated controls (Han et al., 2015; Han et al., 2017; but not in Swiss-derived male mice: Yap and Miczek, 2007). Extensive parametric studies in rats identify four brief episodes of social defeat stress over the course of ten days as necessary and sufficient to prolong cocaine self-administration during a 24 h binge (Boyson et al. 2011, 2014; Covington et al., 2008; Covington and Miczek 2001, 2005; Cruz et al., 2011; Holly et al. 2015, 2016; Leonard et al., 2017; Miczek et al., 2011; Miczek and Mutschler, 1996; Quadros and Miczek, 2009; Yap et al., 2015).

Though several studies characterize the effects of social defeat stress on cocaine-taking in female rats, cocaine-taking has yet to be studied in defeated female mice. Female rats that are ***intermittently*** defeated four times over the course of 10 days by an aggressive, lactating female resident show a greater locomotor sensitization to acutely administered cocaine compared to males and a sustained increase in accumbal dopamine in response to cocaine. This effect of cocaine on locomotor sensitization is most apparent in defeated females tested in estrus (Holly et al., 2012). A spike in circulating estradiol during this phase may be associated with increased cocaine-induced dopamine signaling, suggesting that the trajectory of future cocaine-taking may depend on interactions between stress history and the estrous or menstrual cycle phase during the initial drug-taking experience (Calipari et al., 2017; Carroll et al., 2004; Lynch et al. 2000, 2001). Given unlimited access, intermittently defeated female rats take cocaine for a longer duration compared to control females and stressed or non-stressed males (Holly et al., 2012). Importantly, socially defeated males and females self-administer cocaine similarly during 30 min sessions (Haney et al., 1995); dysregulated, persistent self-administration by socially defeated females only becomes apparent when animals are given unlimited access (Holly et al., 2012), indicating that intermittent social defeat stress may impair neural mechanisms that regulate the cessation of drug-taking.

In a ***continuous*** defeat protocol, stressed females are defeated by lactating dams during 30 min episodes, occurring twice daily for 21 consecutive days. Stressed animals are then housed in protective cages in an aggressive resident's home cage during the periods between defeat experiences (Shimamoto et al. 2011, 2015). In contrast with the escalation in cocaine-taking observed in intermittently stressed females, a significant subset of continuously defeated females exhibits low saccharin preference and reduced cocaine self-administration compared to controls (i.e., an anhedonic phenotype; Shimamoto et al., 2015). The remaining defeated females display a significant saccharin preference and increases in cocaine self-administration compared to anhedonic individuals. Interestingly, non-defeated and anhedonic females demonstrate the expected cocaine-induced increase in accumbal dopamine whereas non-anhedonic stressed females have a substantially blunted dopamine response to acutely administered cocaine

(Shimamoto et al., 2015). While intermittently stressed females likely take more cocaine due to an increase in the drug's rewarding effects (Holly et al., 2012), continuously defeated females may increase their drug-taking due to a suppression in cocaine's rewarding effects (Shimamoto et al., 2015).

These studies provide insight into a possible dopaminergic mechanism that may escalate cocaine self-administration through a shift from positive to negative reinforcement in continuously defeated female rats (Koob and Le Moal, 2008). Due to the prevalence of comorbid substance use and mood disorders in women, potential therapeutic interventions need to be tested using similar translational models of escalated drug self-administration in socially defeated female mice and rats.

3.2.3. Opioids

Among men and women, there has been a rapid increase in the rate of non-medical prescription opioid use and related overdose fatalities as well as a fivefold increase in deaths due to heroin overdoses (Centers for Disease Control and Prevention, 2017; Hall et al., 2008; Paulozzi et al., 2011; Substance Abuse and Mental Health Services Administration, 2013). Women are more likely than men to begin drug use with a valid medical prescription (McHugh et al., 2013), and unlike cocaine, heroin or alcohol, prescription opiate abuse is equally prevalent in men and women (Back et al., 2010; Green et al., 2009). The onset of heroin use among women is strongly associated with heroin use by a sexual partner whereas men tend to receive their first injection from a friend (Frajzyngier et al., 2007). It is apparent that different factors increase the risk of initiating opiate abuse in men and women; likewise, gender may also predict the trajectory of opiate abuse (Back et al., 2011; Hernandez-Avila et al., 2004) and treatment outcome (Greenfield et al., 2010; Jones et al., 2005; Najavits et al., 2007; Unger et al., 2010).

Nearly a quarter of non-medical prescription opioid users report psychological distress, with significantly higher rates among women relative to men (Back et al., 2010) Consistently, women are more likely to have co-occurring psychological and opioid use disorders than men (Back et al., 2010; Green et al., 2009) and women are more likely to abuse prescription opiates due to emotional issues and affective distress (Jamison et al., 2010). While numerous studies report sex-dependent interactions between stress and drugs of abuse (Fox and Sinha, 2009), only a handful of clinical and preclinical studies investigate the sex-dependent effects of social stress on prescription opiate and heroin abuse.

In one of the few related preclinical investigations, Laredo et al. (2015) report that intermittent social defeat stress by a same-sex aggressive resident impedes subsequent behavioral flexibility and down-regulates μ-opioid receptor binding in the orbitofrontal cortex of male California mice (*Peromyscus californicus*). In contrast, female California mice are insensitive to these effects of social defeat stress. Behavioral flexibility, or the capacity for behavioral adjustment in response to changes in external or internal stimuli, may correlate with the initiation and continuation of drug use, the effectiveness of specific interventions and the likelihood of maintained abstinence (Winstanley et al., 2010; Zilverstand et al., 2018). Particularly in males, social stress-induced behavioral inflexibility and changes in μ-opioid receptor expression may maintain drug consumption, and cognitive interventions in conjunction with pharmacotherapy may be ideal for targeting the inflexible behaviors that contribute to compulsive drug use (Konova et al., 2013; Zilverstand et al., 2018). The behavioral and neural mechanisms that promote sex differences in the trajectory of opioid abuse demand additional investigation, particularly in male and female drug users with a significant history of social stress and in male and female rodent social defeat stress models.

4. Stress-induced neuroplasticity and increased drug use

Social stress during acute confrontations persistently activates neural and endocrine processes that promote drug-seeking and taking. Increasing the duration and frequency of stress exposure can yield neuroadaptations that result in long-term changes in neural and behavioral responses to drugs of abuse. While noradrenergic and serotonergic projections have been the focus of many studies (Der-Avakian et al., 2014; Maier and Watkins, 2005; Valentino and Van Bockstaele, 2008), the mesocorticolimbic dopamine system has garnered significant attention because it is both recruited by stress (Imperato et al., 1989) and required for the reinforcing effects of alcohol (Imperato and DiChiara, 1986), cocaine (de Wit and Wise, 1977) and other drugs of abuse (DiChiara and Imperato, 1988). During an aggressive confrontation with a dominant male, subordinate animals show a marked increase in burst firing within a subset of VTA dopamine neurons (Anstrom et al., 2009; Barik et al., 2013). Accordingly, social stress increases extracellular dopamine release within the NAc and mPFC (Barik et al., 2013; Han et al., 2015; Holly et al., 2015; Tidey and Miczek 1996, 1997), and this increase is greatest in rats with prior stress experience. These findings suggest that repeated exposure to social stress can induce adaptive modifications in mesocorticolimbic dopamine activity to escalate alcohol and psychostimulant intake.

An array of peptide signaling systems are mobilized in response to perceived threat and many of these converge on mesocorticolimbic pathways in order to coordinate adaptive coping behaviors. Recurring exposure to social stress persistently alters several peptide and hormone signaling systems that have been implicated in cocaine or alcohol abuse (e.g., opioids, glucocorticoids, orexin, oxytocin, corticotropin releasing factor, urocortin; Golden et al., 2011; Holly et al., 2016; Litvin et al., 2011; Nikulina et al., 1999; Nocjar et al., 2012). Among these, CRF has been comprehensively studied as a candidate target for the interactions between stress and drug abuse (Koob, 2010). Briefly, the CRF/urocortin system mediates several behavioral and physiological effects of psychostimulants (Lodge and Grace, 2005; Lu et al., 2003) and alcohol (Funk et al., 2007; Ryabinin et al., 2002; Valdez et al., 2002; Zorrilla et al., 2014), and may exert control over appetitive behavior through direct modulation of dopamine neurotransmission in both the VTA (Ungless et al., 2003; Wanat et al. 2008, 2013) and NAc (Lemos et al., 2012; Peciña et al., 2006).

4.1. Alcohol

Exposure to repeated stress can increase neural and behavioral responding to future stimuli that similarly engage mesocorticolimbic dopamine circuitry. This mechanism may enhance drug abuse vulnerability in a subset of individuals who are exposed to episodic social defeat stress. In mice, cross-sensitization between defeat stress and alcohol leads to significant changes in accumbal dopamine release; in response to a low dose of alcohol (0.1 g/kg), repeatedly defeated animals show an increase in evoked dopamine release (Yavich and Tiihonen, 2000) while higher doses (2.0 g/kg) reduce dopamine overflow (Deal et al., 2018; Yavich and Tiihonen, 2000). Stress-induced neuroadaptations may alter the rewarding effects of alcohol to increase drinking in socially defeated individuals.

Some neuropeptides, including CRF, can modulate mesocorticolimbic dopamine release, causing lasting neural changes that may lead to stress-escalated alcohol drinking (Hwa et al., 2016a; Ostroumov et al., 2016). Following ten days of continuous social defeat stress, male B6 mice exhibit a unique pattern of chronically elevated regional brain activation along with an increase in repeatedly activated cells, as determined by manganese-enhanced magnetic resonance imaging and ΔFosB immunohistochemistry, respectively. These markers of increased activity are detected in brain areas such as the prefrontal cortex, ventral hippocampus, and also in the bed nucleus of the stria terminalis (BNST; Laine et al., 2017). Crosstalk between neural circuits involved in stress and reward processing may rely on networks in the BNST and central amygdala (CeA; Erb and Stewart, 1999; Lebow and Chen, 2016; Silberman et al., 2013). Novel populations of CRF-expressing,

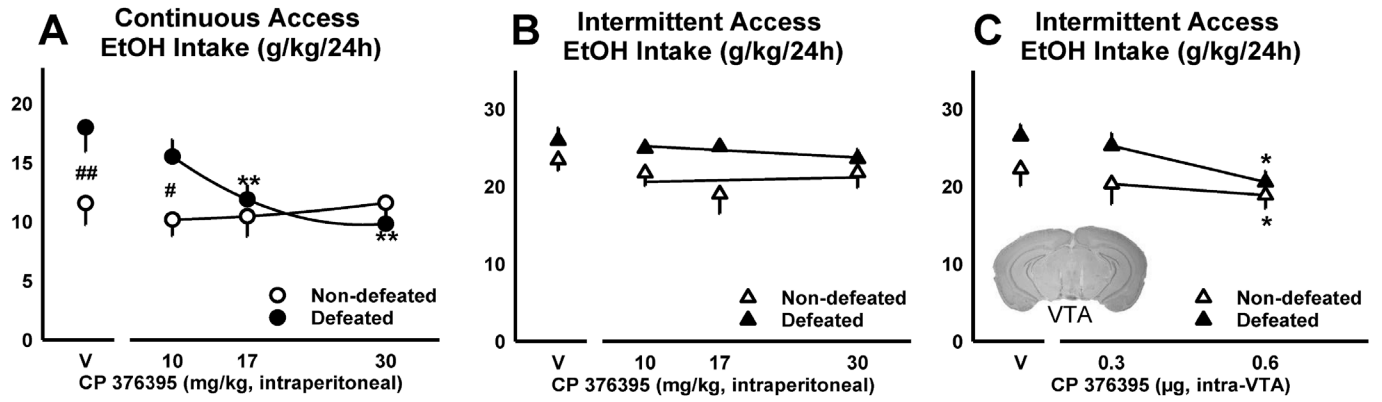

Fig. 3. Daily alcohol intake (g/kg/24 h) shown as mean ± SEM for socially defeated and non-defeated C57BL/6J males with either (A) continuous or (B, C) intermittent access to alcohol. Mice were treated with doses of the CRF-R1 antagonist, CP376395, via systemic injections (A, B; adapted from Newman et al., 2018), or via microinfusions, delivered directly into the ventral tegmental area (VTA; C; adapted from Hwa et al., 2016a). Best-fit curves are in black. $*p < 0.05$, $**p < 0.01$ vehicle vs. drug; $\#p < 0.05$, $\#\#p < 0.01$ non-defeated vs. defeated.

GABAergic spiny projection neurons extend directly from either the CeA or the anterior BNST to the VTA (Dedic et al., 2018). These cells are characterized in part by their expression of calcium/calmodulin-dependent protein kinase 2α, which is involved in synaptic plasticity and may render these projection neurons particularly susceptible to long-lasting effects of social defeat stress on dopamine signaling (Licata and Pierce, 2003; Lisman et al., 2002; Robison, 2014).

In male B6 mice, systemic or intra-VTA injections of the CRF-R1 antagonist, CP376395, can transiently reduce alcohol consumption in intermittently defeated and non-defeated mice during the initial four hours of intermittent or continuous access to 20% EtOH (Hwa et al. 2016a, 2016b; Newman et al., 2018). In contrast, only systemically administered CP376395 selectively reduces social stress-escalated drinking for 24 h, specifically in mice with continuous access to alcohol (Fig. 3; Newman et al., 2018). These findings reveal that CRF-R1 antagonists likely produce their social stress-specific effects on alcohol intake by acting outside of the VTA (Newman et al., 2018). In addition, the intermittent access to alcohol protocol, which escalates drinking and alcohol preference by alternating between days of alcohol access and days of forced abstinence (Fig. 1; Hwa et al., 2011), seems to prevent CRF-R1 antagonists from producing long-lasting, social defeat stress-specific effects on drinking (Fig. 3).

Interestingly, when B6 males are administered CP376395 into the BNST, only non-defeated mice reduce their continuous access alcohol intake and, while a history of intermittent defeat stress increases BNST *CRH* mRNA, CRF-R1 transcript remains unaltered (Albrechet-Souza et al., 2017). If protein levels parallel mRNA expression data, this could signify a social defeat stress-induced increase in CRF content in GABAergic, VTA-projecting BNST neurons (Dedic et al., 2018). Such mechanisms require additional exploration, as it appears that both social defeat stress and the pattern of alcohol intake produce changes in CRF/CRF-R1 signaling that determine the effectiveness of CRF-R1 antagonists.

Regarding sex differences, studies identify dimorphic patterns of extrahypothalamic CRF signaling in male versus female rats. The extent to which CRF action on CRF-R1 results in receptor internalization is significantly greater in males than in females, indicating that females may be subject to greater levels of basal CRF activity due to a less responsive, cellular negative feedback mechanism (in locus coeruleus: Bangasser et al., 2010; Curtis et al., 2006; Valentino et al., 2013). Acute stress-induced release of CRF prompts CRF-R1 binding with β-arrestin 2, which promotes receptor internalization in males, but not in females. This may serve as an underlying mechanism for increased susceptibility to stress-related psychopathologies in females, and may explain some sex-specific effects of drugs that target the CRF system (Becker and Koob, 2016; Valentino et al., 2013).

Though antagonism of CRF-R1 selectively suppresses social defeat stress-escalated alcohol drinking in male B6 mice (Fig. 3A; Newman et al., 2018), CP376395 does not reduce stress-escalated alcohol consumption in defeated B6 females (Newman et al. in prep). The CRF-R1 antagonist verucerfont was similarly ineffective in suppressing alcohol craving in abstaining, alcohol-dependent women following evaluation stress during the TSST (Schwandt et al., 2016). While CRF-R1 antagonism may be effective in treating ongoing, excessive alcohol consumption in defeated males, it may be more appropriate to address reduced negative feedback of CRF signaling in socially stressed females. Dimorphic patterns of CRF-R1 trafficking in response to stress require further investigation using male and female mouse models of social defeat stress-escalated alcohol drinking, with a focus on brain areas characterized as sexually dimorphic.

4.2. Cocaine

Episodic exposure to social defeat stress results in a profound sensitization to salient behavioral and neurochemical consequences of cocaine administration. An extensive literature demonstrates that social defeat stress can potentiate the motor stimulant effects of cocaine or *d*-amphetamine for months after the final defeat experience (Boyson et al. 2011, 2014; Covington et al., 2005; Covington and Miczek, 2001; Han et al., 2015; Holly et al., 2012; Miczek et al. 1999a, 1999b; Nikulina et al. 1998, 2004; Yap et al., 2005). Similar effects can be observed after chronic cocaine administration, suggesting that stress and drug exposure may induce behavioral sensitization through similar mechanisms (footshock stress: Herman et al., 1984; MacLennan and Maier, 1983). Indeed, in vivo microdialysis studies indicate that defeat-induced locomotor sensitization parallels changes to the neurochemical response to cocaine within mesolimbic dopamine circuits. Specifically, experience with intermittent social defeat stress potentiates cocaine or amphetamine-induced dopamine release within the NAc of rats and mice (Boyson et al., 2014; Han et al., 2015; Holly et al., 2012; Miczek et al., 2011).

Stressors may facilitate glutamatergic synaptic plasticity within the VTA, thereby strengthening associations between drugs of abuse and drug-predictive cues (Robinson and Berridge, 1993; Vanderschuren and Kalivas, 2000). Intermittent social defeat stress can enhance NMDA receptor-mediated long term potentiation (LTP) by increasing IP_3R sensitivity in VTA dopamine neurons (Stelly et al., 2016). Glutamatergic synapses in the VTA are more readily strengthened during a 30-day period after stress exposure, and during this time, rats show enhanced acquisition of cocaine-induced CPP (Stelly et al., 2016). Interestingly, in rats, pharmacological inhibition of VTA NMDA receptors during social defeat can prevent the induction of locomotor

sensitization and can block the effects of stress on cocaine self-administration during a binge (Covington et al., 2008). Certain activity-dependent changes in cellular states can increase the probability of LTP (Abraham, 2008); this type of metaplasticity may promote drug-paired contextual cue learning and blocking this phenomenon may serve as a promising direction for therapeutic interventions targeting cocaine addiction and relapse.

CRF signaling is critical for the long-term maladaptive consequences of social stress on cocaine self-administration and appears to play an important role in the acute initiation of drug-seeking behavior (Blacktop et al., 2011; Specio et al., 2008; Wang et al., 2005). A single social defeat experience elicits a robust but transient phasic increase in extracellular CRF within the posterior VTA. In animals with a history of repeated social defeat stress, the CRF response to social stress or cocaine is enhanced and basal CRF concentrations become and remain tonically elevated throughout the VTA (Han et al., 2017; Holly et al., 2016). Elevated CRF tone may interact with mesolimbic DA outputs to augment later stress- or cocaine-dependent behavioral responses. Indeed, defeat-experienced animals demonstrate escalated rates of cocaine self-administration (Han et al., 2017) and show a robust context-induced reinstatement of cocaine seeking compared to control animals (Fig. 2G; Holly et al., 2016). Importantly, both of these effects can be attenuated with compounds that antagonize CRF signaling (Fig. 4D).

These findings collectively suggest that social defeat engenders a neural state that is conducive to relapse-like behavior, and that maladaptive cocaine-dependent behavior can be ***reversed*** by the blockade of CRF receptors in the VTA (Fig. 4C-D). In support of this hypothesis, application of CRF receptor antagonists are also sufficient to ***prevent*** the behavioral consequences of intermittent stress on subsequent cocaine self-administration (Fig. 4A-B). Intra-VTA microinfusions of either CRF-R1 or CRF-R2 antagonists prior to social stress episodes prevent stress-escalated drug-taking (Boyson et al. 2011, 2014; Burke and Miczek, 2015; Han et al., 2017). On the other hand, exogenous CRF administration in place of social defeat only partially reproduces the behavioral effects of stress on drug-taking (Leonard et al., 2017). Rats that receive repeated deliveries of CRF into the VTA exhibit a pattern of cocaine self-administration that is relatively inelastic to changes in response cost which may reflect more discrete changes in effort-related responding. CRF-treated rats do not, however, engage in prolonged cocaine binges in a pattern that is characteristic of stress-experienced animals. In sum, patterns of cocaine self-administration differ between stress-experienced animals and CRF-treated animals, highlighting the importance of identifying precise behavioral deficits that tie CRF to social defeat stress-induced neuroadaptations.

4.3. Opioids

Stress-sensitive, noradrenergic cells in the locus coeruleus (LC) are regulated, in part, by CRF and the endogenous opioid, enkephalin. Acting via CRF-R1 and μ-opioid receptors, respectively, these neuropeptides have opposing effects; while CRF increases LC discharge rate, enkephalin reduces LC activity (Valentino and Van Bockstaele, 2008). In male rats, exposure to repeated social defeat stress produces a delayed-onset reduction in neural firing of LC cells, indicating a shift from balanced opioid and CRF signaling in favor of preferential opioid receptor activation (Chaijale et al., 2013). For at least two weeks after the final social defeat experience, treatment with the competitive opioid receptor antagonist, naloxone, engenders a significant increase in LC

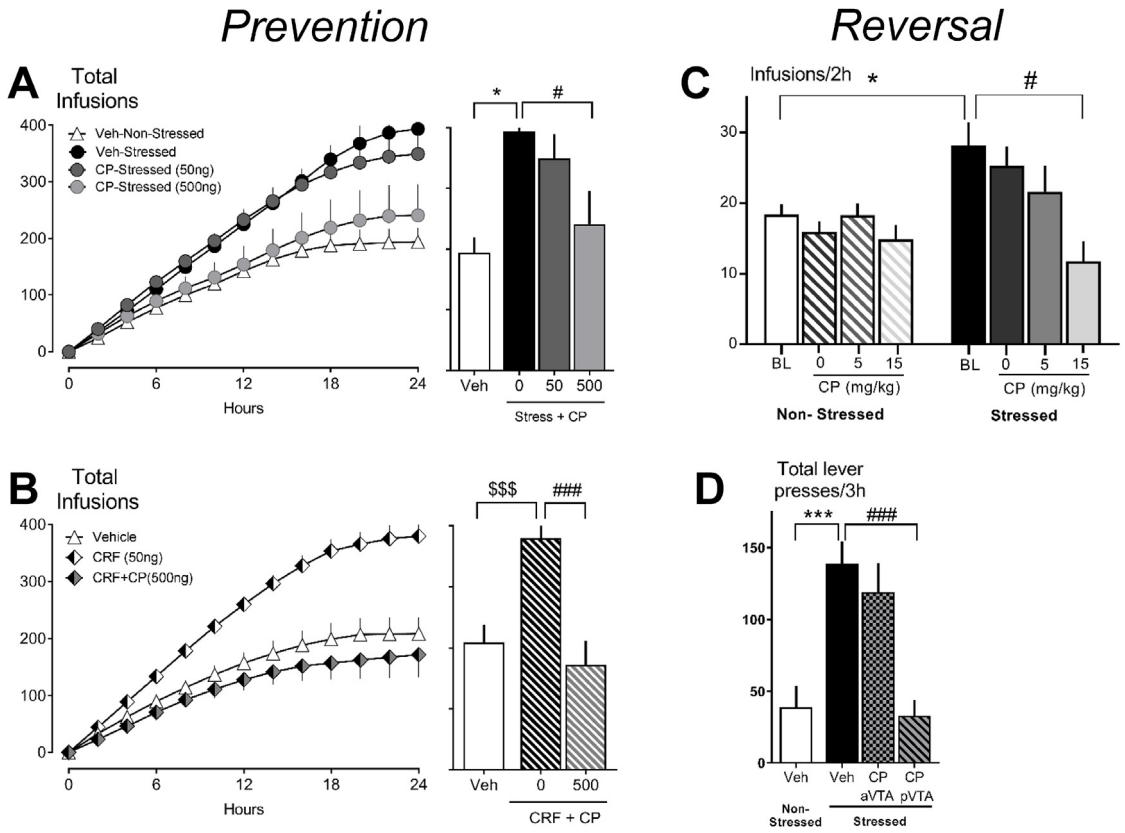

Fig. 4. The CRF-R1 antagonist, CP376395 prevents escalated cocaine consumption across a 24 h "binge" when administered prior to (A) social defeat stress or (B) prior to intra-VTA microinfusion of CRF; total number of cocaine infusions (0.3 mg/kg) across a 24 h shown as mean ± SEM. (A, adapted from Boyson et al., 2014; B, adapted from Leonard et al., 2017); and acute treatment with CP376395 reverses stress-escalated (C) cocaine intake during a 2 h access session or (D) cocaine-seeking responses during context-induced reinstatement (C, adapted from Han et al., 2017; D, adapted from Holly et al., 2016). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ non-defeated vs. defeated; \$$p < 0.05$, \$\$$p < 0.01$, \$\$\$$p < 0.001$ vehicle-microinfusion vs. CRF-microinfusion; #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ vehicle vs. CP376395.

activity, specifically in stressed rats. Through its rapid, competitive binding to opioid receptors, naloxone disinhibits the LC and reveals a substantial upregulation in opioid receptor-mediated suppression of LC discharge (Chaijale et al., 2013). These cellular effects are observed in conjunction with somatic signs of opioid withdrawal including teeth chattering and body shakes. In addition, repeated social defeats can increase LC firing in response to reward, indicating augmented reward salience in stressed animals (Chaijale et al., 2015). These findings suggest that individuals with a history of social defeat stress may experience a withdrawal-like state and may preferentially allocate attentional resources toward rewarding stimuli; future studies will determine whether this phenotype also promotes escalated opiate self-administration (Chaijale et al., 2013, but Cruz et al., 2011).

The development of adaptive coping behaviors likely contributes to the severity of perceived stress, and can reduce the affective consequences of stress-related psychopathologies (i.e. anxiety, depression, posttraumatic stress disorder; Wood and Bhatnagar, 2015). In rats, coping strategy in response to social defeat stress exposure can be distinguished based on the latency to submit by the male intruder during a resident-intruder confrontation. Rats characterized as short-latency (SL) responders exhibit a depressive-like, stress-vulnerable phenotype while long-latency (LL) individuals do not show anhedonic-like behavior and are therefore deemed stress-resilient (Wood et al. 2010, 2012, 2015). Interestingly, all rats are SL responders during their initial defeat experience, suggesting that through repeated stress exposure, a subset of rats eventually shows the resilient-like phenotype (i.e., LL; Reyes et al., 2015). A thorough characterization of LC afferents provides evidence for two, divergent patterns of neuroadaptations in response to repeated social defeat stress exposure. While SL rats display an increase in the activation of central amygdala CRF projections to the LC and a suppression of enkephalin-positive LC afferents, LL rats show the opposite pattern of cellular activation with a suppression in CRF signaling and greater LC innervation by enkephalin-positive projections (Reyes et al., 2015). Though LL rats are stress-resilient in the context of depressive-like behaviors, this subgroup may be more susceptible to increased opiate consumption due to negative reinforcement, resulting from a potential withdrawal-like state (Chaijale et al., 2013; Koob, 2008). Further work should explore whether opioid self-administration selectively increases in SL or LL rats.

5. Conclusions

For a broad range of mammalian species, social stress represents a unique ethological challenge. In rodent models, recurring exposure to social defeat appears to produce a distinct profile of neuroadaptations that translates most readily to the repercussions of social stress in humans (Golden et al., 2011; Miczek et al., 2008). Varying the length of exposure to social threats and attacks can have divergent effects on behavioral and neural outcomes. Brief intermittent episodes of social stress often escalate ethanol and cocaine intake, particularly under extended access conditions. Conversely, continuous exposure to social stress often suppresses cocaine intake in rats, though continuous and chronic stress can escalate alcohol drinking in male and female mice. The direct connection between social stress experience and subsequent changes in drug-taking illustrates a potential role for extrahypothalamic CRF and mesocorticolimbic dopamine.

Stress-induced neuroadaptations in CRF modulation of monoamines are key candidate mechanisms for social defeat stress to escalate alcohol consumption and cocaine self-administration. As demonstrated by the selective effects of CRF-R1 antagonists in socially defeated mice (Fig. 3A; Newman et al., 2018) and rats (Boyson et al. 2011, 2014; Burke and Miczek, 2015; Han et al., 2017), CRF likely plays a critical role in stress-escalated drug-taking. However, presynaptic CRF or urocortin release in conjunction with a primary neurotransmitter, such as glutamate or GABA, may ultimately shape neuroplasticity in post-synaptic monoaminergic cells. Therefore, investigating presynaptic and synaptic interactions between CRF and amino acid neurotransmitters (e.g., co-storage, co-release, modes of synaptic plasticity) may reveal stress-induced changes in co-release mechanisms to yield more effective and targeted therapeutic options.

This review focuses primarily on drug consumption in animals that are repeatedly ***defeated***; however, a growing body of literature also demonstrates the intensely reinforcing effects of ***winning*** aggressive encounters (Aleyasin et al., 2018b). Aggressive male mice will work for the opportunity to attack a submissive intruder (Covington et al., 2018; Fish et al. 2002, 2005; Golden et al., 2017b), and will also favor an aggression-paired chamber during CPP testing (Aleyasin et al., 2018a; Golden et al., 2017a). Repeatedly winning aggressive encounters may upregulate dopamine signaling, thereby increasing the incentive to win subsequent confrontations (Becker and Marler, 2015; Couppis and Kennedy, 2008; Filipenko et al., 2001; Kudryavtseva et al., 1999; Schwartzer et al., 2013). Neuroadaptations in dopamine signaling could also render victorious individuals more sensitive to the pro-aggressive effects of alcohol; indeed, aggressive male B6 residents that are repeatedly treated with alcohol show a robust increase in their motivation to engage in future, aggressive encounters (Covington et al., 2018). Additional studies are necessary to illuminate how repeatedly winning aggressive encounters might influence dopaminergic transmission and subsequent, voluntary drug consumption.

While most preclinical studies of social defeat stress evaluate defeated males, recently developed protocols in socially defeated female mice will be instructive for drug self-administration research (Harris et al., 2018; Takahashi et al., 2017; Newman et al. in prep). Considering the overwhelming prevalence of comorbid substance use and mood disorders in women, there is a significant demand for research that investigates the molecular, neural and chemical mechanisms that link sex to stress-related psychopathologies. To advance the targeted manipulation of stress-sensitive cell populations, sex-dependent neuroadaptations to social defeat stress must be thoroughly characterized using cell- and pathway-specific genetic techniques applied to sexually dimorphic brain regions such as the BNST and LC.

Social stress exposure largely increases the risk of drug abuse in both clinical and preclinical populations; however, only a subset of individuals with a history of social stress exhibits stress-escalated drug-taking. Substantial individual variability in stress-related behavioral outcomes suggests that discrete psychobiological factors contribute to the overall pathological impact of a given stressor (de Boer et al., 2017; Feder et al., 2009). While distinct behavioral phenotypes may be useful in predicting or assessing stress vulnerability, stress susceptibility and resilience should be considered in the context of specific dependent variables or experimental endpoints. For instance, although active coping during social stress encounters tends to predict resilience to depressive-like behaviors in rats (Wood et al., 2010), individuals that actively engage with dominant aggressors tend to exhibit increased binge-like cocaine self-administration (Boyson et al., 2016) and more pronounced drug-seeking in response to an acute stress experience (Manvich et al., 2016). Similarly, female rats characterized as stress-susceptible according to their anhedonic-like profile of saccharin preference subsequently self-administer less cocaine than their non-anhedonic counterparts, suggesting a stress-resilient drug-taking phenotype (Shimamoto et al., 2015). In terms of alcohol, socially defeated male mice that display a depressive-like phenotype during social interaction testing subsequently consume more alcohol than stress-resilient animals (Nelson et al., 2018), indicating that stress-escalated drinking and depressive-like behaviors may share some underlying biological mechanisms. These observations highlight the demand for further investigations that characterize the specific behavioral and biological factors that predict vulnerability to distinct, stress-related psychopathologies, including drug and alcohol use disorders.

6. Summary highlights

- Both the pattern of social defeat stress and drug access influence the effects of social stress on drug consumption, and there is strong evidence that these conditions are drug-specific.
- Animal models of repeated or continuous social defeat stress can persistently and preferentially escalate voluntary alcohol consumption when the onset of alcohol access occurs days after the final stress episode.
- Repeated episodic social defeat stress can increase measures of cocaine self-administration in rats given unrestricted access to cocaine during a 24–48 h long binge. By contrast, exposure to continuous stress tends to suppress cocaine-taking in stress-vulnerable individuals.
- The incidence of drug abuse is increasing, particularly among women. Newly developed preclinical models can be used to evaluate the sexually dimorphic effects of social defeat stress on pathological drug consumption.
- Neural adaptations that promote the escalation of drug-taking in the hours, days or weeks following a social defeat experience may involve changes in tonic CRF and in CRF modulation of mesocorticolimbic dopamine signaling.

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