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Effect of Early Life Social Adversity on Drug Abuse Vulnerability: Focus on Corticotropin-Releasing Factor and Oxytocin

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Abstract

Early life adversity can set the trajectory for later psychiatric disorders, including substance use disorders. There are a host of neurobiological factors that may play a role in the negative trajectory. The current review examines preclinical evidence suggesting that early life adversity specifically involving social factors (maternal separation, adolescent social isolation and adolescent social defeat) may influence drug abuse vulnerability by strengthening corticotropin-releasing factor (CRF) systems and weakening oxytocin (OT) systems. In adulthood, pharmacological and genetic evidence indicates that both CRF and OT systems are directly involved in drug reward processes. With early life adversity, numerous studies show an increase in drug abuse vulnerability measured in adulthood, along a concomitant strengthening of CRF systems and a weakening of OT systems. Mechanistic studies, while relatively few in number, are generally consistent with the theme that strengthened CRF systems and weakened OT systems mediate, at least in part, the link between early life adversity and drug abuse vulnerability. Establishing a direct role of CRF and OT in mediating the relation between early life social stressors and drug abuse vulnerability will inform clinical researchers and practitioners toward the development of intervention strategies to reduce risk among those suffering from early life adversities.

Keywords

Maternal separation; social isolation; social defeat; corticotropin-releasing factor; oxytocin; conditioned place preference; self-administration

Introduction

Early life events involving adverse social experiences may alter neuronal development and drive the behavioral expression of increased drug abuse vulnerability. This review focuses on preclinical models of maternal separation, social isolation, and social defeat as key models of early life adversity that have an extensive literature base. While each of these

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developmental models undoubtedly involve multiple neural mechanisms, we will focus on corticotropin-releasing factor (CRF) and oxytocin (OT) systems as key mediating mechanisms for driving increased risk in adulthood. CRF is chosen because early life adversity is thought to activate stress systems, while OT is chosen because of its known role in maternal behavior, pair bonding, social reward, and social recognition. Moreover, clinical literature suggests that early life problems with social attachment alter CRF and OT systems that interact with reward-relevant dopamine pathways involved in addiction (Strathearn et al., 2019).

The main theme to be advanced is that early life adversity increases drug abuse vulnerability later in life because such adversity causes, at least in part, a strengthening of CRF systems and a weakening of OT systems. The oppositional effect of early life adversity on these two neuropeptides is consistent with evidence pointing to an inverse relationship between CRF and OT systems (Neal et al., 2018), with CRF activation triggering the hypothalamic-pituitary-adrenal (HPA) stress axis and OT activation having a buffering effect on this activation (Heinrichs et al., 2003; Smith and Wang, 2014). The sections of the review are organized as follows: *First,* we establish in adults that CRF activation increases and OT activation decreases drug abuse vulnerability. *Second,* after briefly describing the normal development of CRF and OT systems, we show that early life adversity strengthens CRF systems and weakens OT systems measured in adulthood. *Third,* we show that these same early life adverse events increase drug abuse vulnerability assessed in adulthood. *Finally,* we discuss some key studies that have directly examined the specific mechanistic role of CRF and OT changes which link early life adversity to altered drug abuse vulnerability. Emphasis is placed on preclinical research, with an eye toward translation to humans, including how early life adversity alters the development of CRF and OT systems leading to exaggerated vulnerability in the expression of substance use disorders. Some notable gaps in the literature are identified as prompts for future research.

2. Role of CRF and OT in drug abuse vulnerability in adulthood

2.1. CRF

While a full review of CRF is beyond the scope of this review, we will provide a brief overview of its function [e.g., see (Heck et al., 2018)]. CRF is a 41-amino acid peptide that initiates activation of the HPA stress axis via stimulation of adrenocorticotropic hormone (ACTH) and is intimately involved in social behavior (Hostetler and Ryabinin, 2013) and drug abuse vulnerability (Zorrilla et al., 2014). CRF neurons within the paraventricular nucleus (PVN) of the hypothalamus (Hypo) control ACTH secretion from the anterior pituitary (Pit). Hypothalamic and extra-hypothalamic CRF systems also affect numerous other regions, such as the cortex (Ctx), hippocampus (Hipp), and amygdala (Amyg), as well as midbrain and brainstem structures (Figure 1). The CRF system consists of two primary receptor subtypes (CRF1 and CRF2), and at least 5 endogenous ligands (CRF, urocortin1, urocortin2, urocortin3 and CRFCRF-binding protein). The distribution of CRF receptors and ligands are heterogenous throughout the brain and there are few pharmacological tools that have high selectivity in manipulating a single ligand-system to determine their precise role in social behavior and drug reward. Among the various neuropeptides involved in drug

reward, CRF has received considerable attention due to its known ability to modulate mesolimbic dopamine reward systems (Kelly and Fudge, 2018; Sinha, 2008).

There are a host of studies in adult animals indicating that activation of CRF systems enhances drug reward processes, including reward associated with stimulants, opioids and alcohol (Table 1). With stimulants, the acquisition of conditioned place preference (CPP) produced by cocaine is enhanced by pretreatment with CRF and weakened by pretreatment with the non-selective α-helical CRF antagonist (Lemos et al., 2020). Differential blockade of CRF1 and CRF2 receptors indicates that the effect on cocaine CPP involves primarily CRF1 receptors (Lu et al., 2003). Similarly, CRF1 antagonists are able to decrease cocaine self-administration (SA) in rats at doses that do not alter responding for a non-drug rewards (Nick and Glenn, 2000; Specio et al., 2008); however, this effect does not appear to generalize to monkeys (Broadbear et al., 1999; Mello et al., 2006). In adult rats, CRF1 receptor antagonists are also able to block the increase in cocaine CPP and SA that occurs following social defeat stress (Boyson et al., 2011). Similar to the effects observed with cocaine reward, CRF1 receptor antagonists are able to decrease acquisition of morphine CPP (Lasheras et al., 2015) and SA of heroin (Greenwell et al., 2009; Park et al., 2015).

The pharmacological evidence suggesting CRF activation enhances stimulant reward is corroborated by other studies using direct genetic manipulations. For example, genetic deletion of CRF1 receptors in mice decreases acquisition of cocaine CPP, although this effect is only observed when a high dose of cocaine (20 mg/kg) is used (Contarino et al., 2017). In another study, overexpression of CRF by an adeno-associated virus microinjected directly into nucleus accumbens (NAc) increases nicotine SA in rats (Uribe et al., 2020). Interestingly, in this latter study, the ability of CRF overexpression to enhance the reinforcing effectiveness of nicotine was modulated by ovarian hormones, as females showed a greater effect of CRF overexpression on nicotine SA than males and this sex difference was negated by ovariectomy.

Perhaps the most compelling evidence for CRF-induced enhancement in drug reward is compiled from studies examining alcohol. Pretreatment with a CRF1 receptor antagonist reliably decreases alcohol SA in both rats and mice (Giardino and Ryabinin, 2013; Hwa et al., 2013; Lowery et al., 2010; Robinson et al., 2019). This effect occurs across different alcohol SA paradigms (drinking in the dark, 2-bottle choice, lever pressing with vapor exposure) and across different routes of administration, including systemically, intracerebroventricular (i.c.v.) or directly into medial prefrontal cortex (mPFC), central nucleus of Amyg (CeA), dorsal raphe (DR) and ventral tegmental area (VTA). In contrast, pretreatment with a CRF2 receptor antagonist has no effect on alcohol SA (Robinson et al., 2019); instead, an urocortin3 CRF2 receptor *agonist* decreases alcohol SA. Thus, results from pharmacological studies suggest that CRF1 receptors, rather than CRF2 receptors, mediate alcohol reward, consistent with the role of CRF1 receptors in stimulant reward.

These pharmacological results are bolstered by other studies using genetic manipulations. Genetic polymorphisms of the *Crf1* gene are associated with patterns of alcohol binge drinking in human adolescents (Treutlein et al., 2006) and genetic knockout of CRF1 receptors decreases alcohol SA in mice (Giardino and Ryabinin, 2013). Alcohol SA is also

reduced by optogenetic inactivation of CRF-containing neurons in CeA (Giordano de et al., 2019). Genetically-derived CRF deficient mice also show reduced sensitivity to alcohol, displayed as a reduction in alcohol CPP and a compensatory increase in alcohol SA using 2-bottle choice (Olive et al., 2003). Conversely, CRF overexpression may enhance sensitivity to alcohol, displayed as a compensatory decrease in alcohol SA using 2-bottle choice (Palmer et al., 2004).

CRF regulation of the HPA stress axis also plays a key role in withdrawal following long-term drug exposure (Kreek and Koob, 1998). With acute exposure, cortisol levels are increased by alcohol (Mendelson et al., 1971), nicotine (Kirschbaum et al., 1992), and cocaine (Heesch et al., 1995). However, the HPA axis adapts to chronic nicotine exposure by increasing basal tone and results in more intense withdrawal during early abstinence (Wemm and Sinha, 2019), likely resulting from nicotine's ability to activate the HPA axis via release of CRF and norepinephrine in PVN (Fu et al., 1997; Matta et al., 1990; Okada et al., 2003). Similarly, opioids appear to alter the HPA axis via a change in CRF regulation. For example, former heroin users on methadone maintenance express ACTH plasma levels equal to normal male volunteers after placebo, but they express significantly higher ACTH plasma levels after the administration of high dose of CRF (Schluger et al., 2003). In rodents, i.c.v. administration of a CRF2 receptor antagonist during morphine withdrawal produces a decrease in somatic naloxone-induced withdrawal symptoms (Navarro-Zaragoza et al., 2011). Further, infusion of a CRF2 receptor antagonist also prevents cocaine-induced corticosterone (CORT) release in rodents (Sarnyai et al., 1992). Thus, while CRF1 receptors appear to mediate drug reward, there may be a role for CRF2 receptors in mediating the effects of drug withdrawal on the HPA axis.

Beyond the HPA axis, the bed nucleus of the stria terminalis (BNST) is also an important component of the stress system involved in drug reward and withdrawal. CRF neurons in the BNST receive dopamine signals from the VTA and periaqueductal gray [PAG; (Meloni et al., 2006)]. Cocaine, nicotine, morphine and alcohol all dose-dependently increase extracellular dopamine in the BNST (Carboni et al., 2000). Antagonism of BNST dopamine D1 receptors decreases both alcohol and sucrose SA (Eiler et al., 2003). The BNST sends reciprocal CRF, gamma-aminobutyric acid (GABA), and glutamate signals to VTA dopamine and GABA neurons (Dong and Swanson, 2006; Georges and Aston-Jones, 2001, 2002; Vranjkovic et al., 2017). These BNST CRF neurons play a role in drug abuse vulnerability, rather than local VTA CRF neurons (Vranjkovic et al., 2017). Withdrawal from cocaine, heroin, or alcohol can produce CRF-mediated dysregulation of BNST neurons (Francesconi et al., 2009). Similarly, intra-BNST CRF prior to alcohol exposure increases anxiety associated with alcohol withdrawal, whereas an intra-BNST CRF1 receptor antagonist prevents the increase in alcohol withdrawal-induced anxiety (Huang et al., 2010). These studies indicate that stress-induced CRF release in VTA and BNST may potentiate withdrawal, making it a novel target for pharmaceutical treatments of substance use disorders.

Additional studies suggest that CRF may potentiate stress-induced relapse. Animals with a history of extended access to cocaine reinstate to CRF when it is administered directly into VTA bilaterally (Blacktop et al., 2011). The administration of a CRF1 receptor antagonist

decreases alcohol seeking following footshock-induced reinstatement (Lê et al., 2000). Similarly, CRF antagonists have been shown to attenuate stress-induced reinstatement of CPP following either cocaine or morphine (Lu et al., 2000; Lu et al., 2001). CRF1 receptor antagonists also block return to nicotine taking following a period of abstinence after nicotine escalation (George et al., 2007), further indicating that VTA CRF manipulations can alter behaviors associated with substance abuse. Beyond the VTA, microinjection of CRF into BNST also produces reinstatement of cocaine seeking, whereas microinjection of a CRF1 receptor antagonist into BNST attenuates footshock-induced reinstatement (Erb and Stewart, 1999).

Despite the preclinical evidence for a role in CRF in drug abuse vulnerability and other addictive behaviors (Roberto et al., 2017), translation into clinical treatment strategies has thus far been unsatisfactory. A review of key clinical studies examining the use of CRF1 receptor antagonists for substance use disorders have been largely negative (Shaham and de Wit, 2016). The lack of efficacy may represent inadequacies of the animal models used, as well as limitations on the pharmacological agents tested in terms of either bioavailability at brain CRF1 receptors or activity at CRF1 vs CRF2 receptors in humans (Spierling and Zorrilla, 2017). Downstream from CRF activity, however, there appears to be some promise for glucocorticoid receptor antagonists in ameliorating withdrawal, particularly with alcohol (Vendruscolo et al., 2015). It remains to be determined if pharmacotherapeutic efficacy is achieved in large-scale clinical trials.

2.2. OT

OT is a nonapeptide that has only one known G-coupled protein receptor in brain. Good drug selectivity for the OT receptor is difficult to achieve because it is only 2 amino substitutions removed from the closely related neuropeptide vasopressin. OT-producing cell bodies exist in dense clusters within PVN and supraoptic nucleus (SON) of Hypo, with dispersed cells in accessory nuclei located between PVN and SON (Baribeau and Anagnostou, 2015; Knobloch and Grinevich, 2014), as well as a sparse distribution in other regions such as BNST and Amyg in some species [(Steinman and Trainor, 2017; Wang et al., 1997); Figure 2]. Among the numerous target regions receiving OT input in rat brain (Warfvinge et al., 2020), OT neurons from PVN specifically project to the reward-relevant NAc and VTA (Knobloch et al., 2012; Ross et al., 2009; Xiao et al., 2017). Aside from its important role in milk letdown and uterine contractions in females, OT plays a vital role in various sexual and social behaviors in both males and females (Caldwell, 2017; Jurek and Neumann, 2018). OT levels are increased in NAc during social affiliative behavior (Ross et al., 2009) and OT release increases activity of dopamine neurons (Hung et al., 2017; Peris et al., 2017). While much of the seminal work has been conducted using monogamous prairie voles, evidence from studies using rats also shows that OT enhances the rewarding effect of social interaction (Ramos et al., 2015) and promotes social affiliation (Bowen and McGregor, 2014)

Beyond its role in sexual and social processes, a host of studies indicate that OT activation diminishes drug reward, including reward associated with stimulants, opioids and alcohol (Table 2). With stimulants such as cocaine, methamphetamine and methylphenidate, OT

injected systemically, i.c.v. or intra-NAc consistently decreases the acquisition of CPP and reduces SA in rats and mice (Baracz et al., 2012; Carson et al., 2010; Leong et al., 2016; Qi et al., 2009; Tanda et al., 2017). The OT-induced decrease in stimulant SA is reversed by OT antagonist pretreatment, indicating that OT receptors are involved. In addition, OT decreases the breakpoint on a progressive ratio schedule of methamphetamine SA, albeit only in females (Cox et al., 2013), and in both males and females it decreases the essential value of methamphetamine as expressed by an increase in elasticity (α parameter) using an economic demand analysis (Cox et al., 2017). These results indicate that activation of OT receptors in NAc diminishes the reinforcer effectiveness of stimulants. Additionally, activation of OT receptors is able to attenuate stimulant seeking triggered by a drug prime or drug-associated cue following a period of extinction (Cox et al., 2017; Cox et al., 2013; Everett et al., 2020; Weber et al., 2018).

OT is also involved in opioid reward processes, although the effects are somewhat mixed compared to stimulants. For example, while OT is reported to have no effect on acquisition of morphine CPP (Moaddab et al., 2015), it decreases heroin SA when administered either systemically or intra-NAc (Ibragimov et al., 1987; Kovács et al., 1985; Kovács and Van Ree, 1985). The picture is complicated by another study reporting that OT and an active OT fragment increases heroin SA (Van Ree and De Wied, 1977). However, this latter study pretreated rats with OT only during an atypical 2-day heroin SA preparation, indicating that OT may reduce opioid SA only after it is acquired over a prolonged regimen.

As for alcohol, there is robust evidence for an OT-induced blockade of reward processes measured by both CPP and SA, an effect that is reversed by OT antagonists. This evidence has accumulated using different routes of OT administration (systemic, intranasal, i.c.v. and intra-NAc), different drinking paradigms (2-bottle choice, drinking in the dark and operant lever pressing) and different species [mice, rats and prairie voles; (Bahi, 2015; King et al., 2017; Macfadyen et al., 2016; Peters et al., 2017; Stevenson et al., 2017; Tunstall et al., 2019)]. Consistent with these pharmacological results, overexpression of OT receptors via lentiviral microinjection into NAc also disrupts acquisition of alcohol CPP (Bahi, 2015) and SA (Bahi et al., 2016).

Some clinical evidence points to OT as a potential pharmacotherapy for substance use disorders, although this work is considered exploratory (Lee and Weerts, 2016). While OT does not reduce cue-induced craving in cocaine-dependent human subjects tested in a controlled laboratory setting (Lee et al., 2014), one report found that it reduces cue-elicited craving among tobacco cigarette smokers (Miller et al., 2016). There is also evidence that OT decreases the severity of withdrawal in alcohol-dependent patients undergoing in-patient detoxification (Pedersen et al., 2013), as well as decreasing cue-reactivity observed in Hipp, cingulate gyrus and associated frontal lobe regions using functional magnetic resonance imaging in heavy social drinkers (Anita et al., 2017). However, another study found that OT does not alter the cognitive and performance-impairing effects of alcohol in social drinkers (Vena et al., 2018). One limitation of these exploratory studies is that they rely primarily on acute intranasal delivery of OT and thus, it is unclear how much brain penetration is achieved via the intranasal route and how this bioavailability is affected when OT is administered under a chronic dosing regimen.

2.3 Summary

CRF1 receptor *antagonists* reduce drug CPP, SA and reinstatement, with evidence suggesting a critical role for CRF1 receptors in VTA, RN and mPFC, most notably for alcohol. While CRF2 receptors may be more involved in drug withdrawal, CRF1 receptors specifically in BNST have also been implicated. In contrast, OT and OT *agonists* reduce drug CPP, SA and reinstatement, with evidence suggesting a critical role for these receptors specifically in NAc. Taken together, these results obtained in adults indicate that drug abuse vulnerability is reduced by weakening CRF systems and/or strengthening OT systems. Unfortunately, application of these basic research findings has not yet yielded compelling clinical efficacy in treating substance use disorders.

3. Development of CRF and OT systems

Before describing how early life adversity can produce long-lasting alterations in CRF and OT systems involved in drug reward processes, this section provides a brief overview of the normal development of these systems in brain.

3.1. CRF

The human fetus has a functional HPA axis by the second trimester of pregnancy and is exposed to placental-derived CRF throughout gestation (McLean and Smith, 2001). In rats, CRF is found as early as gestational day 18 in the anterior median eminence (ME) using immunohistochemistry (Bugnon et al., 1982) and CRF mRNA is present as early as gestational day 17 in PVN (Baram and Lerner, 1991; Grino et al., 1989). CRF receptors also appear by the gestational day 17 and reach an overexpressed level by postnatal day (PND) 8. At that point, CRF receptors decrease to their adult densities by PND 21. CRF receptors are distributed widely, being more concentrated in striatum (Str) during the gestational period, while becoming more concentrated in cortex (Ctx) during postnatal development (Insel et al., 1988). While CRF mRNA expression is dense in PVN at gestational days 18–19, it decreases around the time of birth to eventually reach adult levels (Grino et al., 1989). This overexpression pattern of CRF mRNA expression appears to mimic CRF protein levels (Bugnon et al., 1982; Korosi and Baram, 2008).

The negative feedback associated with CRF synthesis in Hypo does not appear to control CRF gene expression during fetal development. Following pharmacological adrenalectomy, pregnant rats show increased CRF mRNA expression, while fetal CRF mRNA expression remains unchanged (Baram and Schultz, 1992). The absence of fetal CRF reactivity is not likely associated with a lack of glucocorticoid receptors, as glucocorticoid receptor mRNA is detected on gestational day 16 (Yi et al., 1994). Further, during postnatal development (PND 4–14), there is a continued stress hypo-responsivity period where CRF receptor numbers and baseline CORT levels are low (Graham et al., 1999), despite the fact that CRF PVN levels may be elevated (Schmidt et al., 2003). During this hypo-responsive period, mild stressors fail to produce an increase in CORT and ACTH release (Schmidt et al., 2003). After the first postnatal week, however, the glucocorticoid negative feedback system begins to exert its effect on CRF mRNA expression (Korosi and Baram, 2008). By postnatal day 16, initial onset of a matured negative feedback system is associated with a decrease in CRF

expression (Schmidt et al., 2003). It is around this time that CRF begins to up-regulate in response to cold-separation stress (Baram et al., 1997). The transient hypo-responsive period during early postnatal development may represent an adaptation that protects against the negative effects of glucocorticoids and CRF in response to some stressors, although this does not appear the case for maternal separation stress (Graham et al., 1999).

Although the glucocorticoid negative feedback system becomes functional on PND 10, CRF regulation via the Amyg remains immature (Korosi and Baram, 2008). In adults, CRF levels are amplified in PVN following repeated stress (Makino et al., 1995). In contrast, even though rats at PND 10 show a heightened CRF mRNA expression in CeA following stress, this effect does not translate into increased CRF mRNA levels in PVN (Hatalski et al., 1998). Further, enhanced CeA CRF expression in adults results in dysregulation of the HPA axis (Keen-Rhinehart et al., 2009), and bilateral lesions of CeA decreases CRF expression in ME (Beaulieu et al., 1989). In contrast, neonatal Amyg lesions in male and female rhesus monkeys produces an increase in daily cortisol secretion and CRF levels in females compared to controls during the prepubertal period (Raper et al., 2014). In humans, evidence suggests that the Amyg may undergo a switch between positive and negative connectivity to the prefrontal cortex (PFC) as children approach adolescence (Gee et al., 2013). Perhaps, during development, the Amyg also shifts between positive and negative connectivity in other areas such as PVN, which may explain differential effects of CeA lesions between neonates and adults on CRF expression and regulation of stress hormones. More research is needed to understand the developmental changes associated with CeA and PVN inter-connections and the regulation of CRF in response to stress across development.

3.2. OT

Given the availability of other recent reviews covering the ontogeny of OT systems in mammalian brain (Baracz et al., 2020; Grinevich et al., 2015; Johnson and Buisman-Pijlman, 2016), only a brief overview is provided here. For humans and rodents, OT neurons are present by the second half of gestation (Altstein and Gainer, 1988; Buijs et al., 1980; Grinevich et al., 2015; Swaab, 1995). In rodents, development of OT neurons progresses rapidly from gestational day 12 to 16 (Grinevich et al., 2015). During this time, the PVN and SON develop cytoarchitecturally, the production of neurophysin-I (OT carrier protein and marker for OT pro-hormone) begins, and an intermediate form of OT becomes detectable. By birth, mature OT is detectable (Altstein and Gainer, 1988) and OT-releasing neurons are present in the accessory nucleus, PVN, and SON (Altman and Bayer, 1978; Grinevich et al., 2015). It is unclear if sex differences exist in the development of OT neurons, but males and females appear to have similar OT synthesis in PVN and SON across species (Dumais and Veenema, 2016). Human fetuses begin producing a mature form of OT relatively early during gestation, starting at 14 weeks, and they express adult-like quantities of OT neurons by approximately gestational week 26 (Swaab, 1995). Although mature OT production is achieved by birth in both rodents and humans (Grinevich et al., 2015), continued maturation of OT systems continues through adolescence.

OT receptors are widely distributed during gestation and they undergo region-specific changes from birth to adulthood, as described in recent reviews (Baracz et al., 2020;

Grinevich et al., 2015). In addition, OT receptor activation can be coupled to either the excitatory Gq or the inhibitory Gi and Go signalling cascades, with the prevalence of each type of G protein being developmentally regulated. For example, by the beginning of adolescence, OT receptor coupling to G_o decreases and G_i coupling begins to emerge, whereas OT receptor coupling to G_q remains ubiquitously distributed (Busnelli and Chini, 2018). Thus, experiences that induce OT release may activate different signalling cascades in an age-dependent manner. Age also moderates OT receptor expression in brain regions important for substance use disorder and social reward, such as NAc and VTA (Baracz and Cornish, 2016; Cox et al., 2017; Dolen et al., 2013; Hung et al., 2017). In NAc, for example, OT receptor binding emerges by PND 10 and peaks at PND 20, prior to the onset of adolescence (Shapiro and Insel, 1989). In VTA, OT receptor mRNA is present at gestational day 15 and peaks at PND 3. Age also affects OT receptor development in other brain regions involved in reward and social learning. For example, in Amyg, OT receptor mRNA is present at gestational day 20 and peaks in adulthood, whereas in BNST, OT receptor mRNA does not emerge until postnatal day 7 and then peaks in adulthood (Yoshimura et al., 1996). Sex differences also exist in OT receptor density during adulthood, with male rats having greater OT receptor density in many forebrain regions, including NAc, BNST, and Amyg, whereas females have greater OT receptor density in Str (Dumais et al., 2013). It is possible that these sex differences are species-specific, but additional work is required in other common laboratory species and in humans to better understand sex differences in OT receptor development (Dumais and Veenema, 2016). Thus, it is important that studies examining environment-induced alterations in OT receptor development consider the age, sex, and brain region under investigation.

Although a high concentration of OT is released within Hypo and spread to nearby regions through passive diffusion (Chini et al., 2017), OT receptor activation in NAc and VTA is likely controlled by direct axonal projections from PVN and SON neurons (Dolen et al., 2013; Grinevich et al., 2016; Hung et al., 2017; Knobloch et al., 2012; Ross et al., 2009). Projections from PVN and SON to Pit emerge during gestational development, and projections from accessory nucleus to Pit are present shortly after birth, but there has been a paucity of research into the ontogenesis of forebrain OT projections (Grinevich et al., 2015; Grinevich and Neumann, 2020). It is hypothesized, however, that development of these projections may continue throughout adolescence (Baracz et al., 2020). Given the OT receptor changes that occur during early life and the putative effects of adolescent development on OT fibers, environmental perturbation by social stressors and other life experiences likely have a lasting impact on OT system development.

3.3 Summary

While both CRF and OT can be detected in PVN and related brain structures prior to birth, there is a continued region-specific maturation of each of these systems into the late adolescent period. In rodents, the negative feedback control of the HPA axis is not expressed fully until almost weaning, and maturation of both CRF and OT neurocircuitries continue throughout adolescence. Thus, perturbations of these developing systems by early life adversity might be expected to produce long-term dysregulations that are manifested behaviorally.

4. Adverse social events during development that alter CRF and OT systems

Considerable clinical evidence indicates that early life social adversity disrupts the normal development of CRF systems, with an overall strengthening of the HPA axis. While changes in CRF systems in brain are difficult to examine directly in humans, the peripheral output signal from the HPA axis measured via salivary or plasma cortisol has been extensively studied. For example, foster children undergoing social neglect display dysregulation of the normal diurnal cortisol rhythm (Blaisdell et al., 2019). In addition, self-reported early life adversity in the pre-school years is associated with elevated CRF levels in cerebrospinal fluid (CSF) in adulthood (Carpenter et al., 2004). Among individuals with personality disorders, scores on the Childhood Trauma Questionnaire are also positively correlated with CRF levels in CSF (Lee et al., 2005). A subsequent study from that same group found that individuals with self-reported problems in parental bonding show elevated CRF levels in CSF (Lee et al., 2006). Corroborating this work in humans, more controlled laboratory studies in non-human primates reveal that adverse early rearing strengthens expression of CRF systems in adulthood (Coplan et al., 1996; Zhang, 2017).

In contrast to the strengthening of CRF systems, clinical literature indicates that early life social adversity produces long-lasting weakening of OT systems. For example, adults who experience high early life stress scores on the Childhood Trauma Questionnaire have decreased OT levels in CSF (Heim et al., 2009), as well as decreased sensitivity to the effect of OT in modulating functional activity of Amyg-PFC neurocircuitry (Fan et al., 2014). These findings are complicated somewhat because there is other evidence that peripheral OT from plasma or saliva is actually *increased* following early life adversity (Leslie et al., 2014; Parker et al., 2009). However, since there is a dissociation between central and peripheral OT systems (Gerald and Falk, 2001), it appears the weakening of OT systems with early life adversity is specific to central nervous system processing. Consistent with this, nursery- or peer-reared monkeys show reduced OT levels in CSF and reduced OT receptor mRNA in brain compared to normal mother-reared monkeys (Maggie et al., 2017; Winslow et al., 2003).

At least 3 major animal models have been widely used to examine the neurobiological mechanisms involved in mediating the long-term effects of early life social adversity, namely maternal separation, social isolation and social defeat (Forster et al., 2018). Importantly, cross-comparison across each of these developmental models sometimes yields conflicting results because they represent qualitatively distinct early life events. In addition, in rodents, each of these developmental models are typically applied at different periods of postnatal development, with maternal separation beginning soon after birth (PND 1), social isolation beginning at weaning (PND 21) and social defeat beginning in late adolescence (PND 28–50). Thus, differences in both how and when each of these developmental models of social adversity are applied implies that direct comparison across different developmental models should be avoided. For example, although maternal separation and social isolation might both be classified as “social deprivation” applied at different developmental periods,

they can lead to opposite effects on the development of dopamine systems expressed in adulthood (Hall, 1998; Hall et al., 1999).

4.1. Maternal separation

Table 3 provides a summary of literature examining the long-term effects of maternal separation on CRF and OT systems. CRF systems are dysregulated by maternal separation models that restrict maternal interaction after the establishment of a mother-child bond (Delavari et al., 2016; O'Malley et al., 2011). Some care in reviewing this field is warranted because a variety of models of maternal separation have been used, including variations in the postnatal interval used to perform the separations, the duration of separations, and the number of separations. Maternal separation results in an immediate elevation of circulating CORT in the rat pup (Ritchey and Hennessy, 1987; Yoshida et al., 2018), as well as a long-lasting hyper-responsivity of the HPA axis to a stressor applied in adulthood, as measured by increased levels of plasma levels of ACTH and CORT (Huot et al., 2001; Roque et al., 2019). The maternal separation-induced change in HPA axis function persists into adulthood and appears resistant to change, as environment enrichment does not normalize the system after the period of maternal separation is terminated. Interestingly, however, if rats are handled *during* the maternal separation period, there appears to be some normalization of CORT release, at least in females (Campbell and Spear, 1999).

Neuroanatomical analyses have also revealed a host of regional brain changes in CRF-related RNA transcripts and proteins following maternal separation. When evaluated at different periods of postnatal development, the acute changes in CRF systems measured in pups immediately following maternal deprivation varies in an age- and region-specific manner, with different regions showing either increased or decreased expression of CRF and CRF receptors (Vazquez et al., 2006a).

At the genetic level, immediately after termination of the maternal separation period, expression of *Crf* and *Crfr1* genes are increased in both Hypo and Hipp (de Almeida Magalhães et al., 2018). Consistent with this, basal CRF production is elevated in major cell body regions such as PVN, BNST, Amyg and Hipp (Aisa et al., 2008; Babygirija et al., 2012; García-Gutiérrez et al., 2016; Hu et al., 2020; Plotsky et al., 2005; Wang et al., 2014), and this elevation is more prominent when maternal separation consists of long (3 hr) rather than short (15 min) durations (Plotsky et al., 2005).

Maternal separation also alters CRF receptor levels. Total CRF receptor binding is increased in PVN (Plotsky et al., 2005), which is attributed primarily to elevated CRF1 receptor mRNA and protein (Aisa et al., 2008; O'Malley et al., 2011). In contrast to the changes in CRF receptor binding in PVN, however, changes in other regions are more complicated. For example, one study found that maternal separation increased CRF1 receptor mRNA in Amyg and DR, while CRF2 receptor mRNA in Amyg, DR and Hipp was decreased (Bravo et al., 2011). It remains to be determined to what extent, if any, these long-term changes at the cellular level are reversible.

In contrast to the strengthening in CRF systems, evidence suggests that maternal separation produces a long-lasting weakening of OT systems, although some results are mixed.

Maternal separation has no effect on plasma OT (Riveros-Barrera and Duenas, 2016; Xu et al., 2018), except for a sex-specific change that does not emerge until adulthood (Riveros-Barrera and Duenas, 2016), where plasma OT decreases in separated males and increases in separated females relative to unstressed controls. In brain, while the total number of OT-containing cell bodies in PVN or SON does not appear altered by maternal separation (He et al., 2018), one report found that magnocellular OT neurons were specifically decreased (Babygirija et al., 2012). This latter finding is bolstered by other reports in rats showing diminished OT mRNA in PVN (Babygirija et al., 2012) and decreased OT in various target structures such as PFC, septum (Sep) and Amyg (Lukas et al., 2010; Oreland et al., 2010; Wei et al., 2020). In voles, there is also a decrease in the number of OT neurons, but only when the dams are exposed to gestational restraint stress (He et al., 2018). Thus, on balance, the overall results point to a diminished strength of OT systems following maternal separation.

Evidence suggests that OT can ameliorate the negative effects of maternal separation. For example, rats that undergo maternal separation have increases in brain derived neurotrophic factor that is normalized by systemic OT treatment (Mansouri et al., 2020a). Increases in pain sensitivity after maternal separation can also be attenuated by systemic (Melchior et al., 2018; Xu et al., 2018) or central (Amini-Khoei et al., 2017a) administration of OT. Administration of i.c.v. OT also reduces depression-like behavior induced by maternal separation (Amini-Khoei et al., 2017b). Guinea pigs that undergo maternal separation in the late preweaning period (PND 20–27) have lower levels of CORT and emit fewer vocalizations after i.c.v. OT (Hennessy et al., 2019). Thus, despite the lack of consistent evidence for effects of maternal stress on the developing endogenous OT system, treatment with OT appears to consistently reduce the negative impact of maternal separation stress.

4.2. Social isolation

Table 4 provides a summary of literature examining the effects of social isolation initiated in adolescence on CRF and OT systems measured in adulthood. Like maternal separation, CRF systems generally are strengthened by adolescent social isolation, which is typically defined by housing animals in single cages with no direct social interaction with conspecifics. Adolescent social isolation increases CRF levels in PVN (Pan et al., 2009; Ruscio et al., 2007) and levels of CRF1 receptor mRNA in Pit (Pinelli et al., 2017). CRF2 receptors expressed in DR are also increased, resulting in altered CRF-regulated serotonergic activity in NAc (Lukkes et al., 2009a; Lukkes et al., 2009c). Further, adolescent social isolation produces heightened anxiety-like behavior in adulthood that is decreased with infusion of a CRF2 receptor antagonist into DR (Bledsoe et al., 2011). In male prairie voles, social isolation for 6 weeks after weaning also induces anxiety-like behavior that is associated with increased CRF mRNA in PVN (Pan et al., 2009).

Consistent with the strengthening of CRF systems, adolescent social isolation produces a downstream enhancement of HPA activity. In particular, long-lasting increases in basal levels of circulating CORT are observed, with application of either a stressor or drug producing a CORT response that is more rapid, but of shorter duration, compared to social-housed controls (Caruso et al., 2014; Lukkes et al., 2009b; Stairs et al., 2011).

The effect of adolescent social isolation on the development of OT systems has been studied in rats, mice, and voles. In general, social isolation weakens development of OT brain systems as reflected in a decreased number of OT cell bodies in PVN, as well as a decreased number of active OT neurons measured by c-Fos immunoreactivity (Tanaka et al., 2019; Tanaka et al., 2010). OT receptor mRNA is also diminished in Hypo and CeA (Han et al., 2018; Pournajafi-Nazarloo et al., 2013), consistent with the general isolation-induced weakening of this brain system. Despite the decrease in number of OT neurons, however, the concentration of OT in PVN is increased (Oliveira et al., 2019; Pan et al., 2009), suggesting that the fewer number of OT neurons exhibit up-regulated synthesis with social isolation. It is not clear if the diminished strength of OT brain systems is reflected by concomitant changes in OT in the periphery. While one study reported decreased plasma OT with social isolation (Harvey et al., 2019), another study reported increased plasma OT (Neal et al., 2018). These conflicting results may reflect a difference in rat strains (Sprague-Dawley vs. Long-Evans); in addition, the latter study was limited to males only (Neal et al., 2018).

4.3. Social defeat

There are several different models of social defeat, including resident-intruder, witnessed social defeat and cage-within-cage resident-intruder (Verbitsky et al., 2020), each which measure hostile and stressful interactions between animals. In adulthood, social defeat is known to strengthen CRF systems (Guo et al., 2020; Han et al., 2017; Holly et al., 2016) and weaken OT systems (Hou et al., 2020; Li et al., 2019). Despite this evidence, however, few studies have confirmed that social defeat during adolescence produces similar changes that last into adulthood. A recent review compiled a list of 20 different studies that have examined adolescent social defeat, but none specifically measured the effects on either CRF or OT systems (McCormick et al., 2017). In one recent study, adolescent social defeat increased CRF2 receptors in DR, but not in other regions such as VTA or locus coeruleus [LC; (Forster et al., 2018)]. However, this finding contrasts with other work showing that CRF2 receptors in DR are *decreased* by maternal separation (Bravo et al., 2011), thus illustrating the differential outcomes obtained with two developmental models of adverse social events applied at different periods of development. With OT, we are aware of only one study examining the effect of adolescent social defeat on OT systems (Ferrer-Perez et al., 2019). In that study, adolescent social defeat did not alter plasma OT. More work is needed to determine if adolescent social defeat alters OT systems in brain.

4.4. Summary

There is considerable evidence that early life adversity alters both CRF and OT systems well into adulthood. With early maternal separation, CRF systems in PVN are enhanced, whereas OT systems in both PVN and Amyg are diminished. A similar pattern appears with postweaning social isolation, with CRF systems strengthened and OT systems weakened. However, even though social defeat applied during adulthood is known to impact both CRF and OT activity, there is a gap in knowledge about the effects of adolescent on CRF and OT brain systems. One study to date does show a strengthening of CRF in DR following adolescent social defeat.

5. Effects of early life social adversity on drug abuse vulnerability

The clinical literature is replete with evidence showing the long-term detrimental effects of early life adversity on long-term physical and psychological health. Regarding substance abuse specifically, physical abuse within the first 5 years of life is predictive of future substance abuse, particularly in females (Lansford et al., 2009). Others have found that stressors induce greater SA of multiple substances of abuse (Sinha, 2008). This final section covers evidence showing that early life social adversity increases drug abuse vulnerability, and describes mechanistic work, albeit limited, that demonstrates a direct role of CRF and OT systems in mediating the relation between early life social adversity and drug abuse vulnerability.

5.1. Maternal separation

Two thorough reviews of the long-term effects of maternal separation on drug reward in preclinical studies have been recently published (Baracz et al., 2020; Walters and Kosten, 2019), and these excellent compilations will not be re-presented here. These reviews provide ample evidence that maternal separation produces reliable increases in morphine reward measured by either CPP or SA, as well as greater CPP and SA using stimulants such as cocaine, amphetamine and methamphetamine; the effect also extends to nicotine CPP (Dalaveri et al., 2017). The general conclusion with opiates and stimulants is supported by results obtained in both mice and rats, as well as across different routes of administration (oral, s.c., i.p. and i.v.). However, these reviews also reveal at least 3 important caveats in the literature. *First,* in contrast to opioids and stimulants, maternal separation has yielded relatively mixed results on alcohol consumption, with some reports showing a reliable effect (Cruz et al., 2008; Portero-Tresserra et al., 2018) and others showing no effect (Marmendal et al., 2004; Vazquez et al., 2006b). The discrepancies in the alcohol literature may reflect procedural differences across studies, with those using longer separation protocols generally showing greater effects (Nylander and Roman, 2013). *Second,* the effect of maternal separation appears to be more reliable when drug reward is tested in adulthood rather than during adolescence, suggesting a period of resilience prior to the observed detrimental effect later in life. *Third,* most studies have been limited to males only and those using both sexes are sometimes underpowered to yield potential sex differences. As one example pointing to sex-dependent effects, maternal separation increases morphine CPP in males, but not females (Michaels and Holtzman, 2008), suggesting females may be buffered from adverse social experiences early in life. Nonetheless, females show long-term increases in excitability of VTA dopamine neurons following maternal separation (Spyrka et al., 2020).

Despite the large number of studies showing enhanced vulnerability to drug abuse following maternal separation, few studies have incorporated analyses of either CRF or OT changes into the study design, thus making it difficult to assess whether changes in these neural systems are associated with changes in CPP or SA. While the two recent reviews compiled over 30 studies examining the effect of maternal separation on drug reward (Baracz et al., 2020; Walters and Kosten, 2019), only 6 studies incorporated a measure of CRF activity and none incorporated a measure of OT activity. Among the 6 studies examining CRF activity, 4 were limited to measuring circulating CORT or ACTH levels as a correlational variable

associated with changes in drug reward (Campbell and Spear, 1999; Faure et al., 2009; Huot et al., 2001; Marmendal et al., 2004), while only 2 measured CRF in brain (Faure et al., 2009; Gondré-Lewis et al., 2016). One report found that maternally separated mice showed exaggerated alcohol consumption in adolescence, which was associated with increased CRF levels in PVN, NAc, and Hipp (Faure et al., 2009); unfortunately, these results were merely correlational.

More recent mechanistic work has begun to examine the specific role of CRF systems in brain in controlling the maternal separation-induced changes in drug reward. In one study, maternal separation facilitated binge alcohol drinking and intracranial infusion of a CRF antagonist into either CeA or mPFC normalized alcohol drinking without affecting sucrose drinking (Gondré-Lewis et al., 2016). Other work has shown that either pharmacological or environment interventions can also normalize the effects of maternal separation on drug reward (Khalaji et al., 2018; Morel et al., 2009), although these latter studies did not assess a specific role for CRF. Nonetheless, these studies together indicate that the effects of maternal separation depend, at least in part, on brain CRF systems and that these effects are modifiable with an intervention.

While similar mechanistic studies have not examined a direct role for OT, there are some relevant studies to draw on. In particular, several studies show that many behavioral deficits induced by maternal separation are ameliorated by OT treatment, including depressive- and autistic-like behaviors (Amini-Khoei et al., 2017b; Ji et al., 2016; Mansouri et al., 2020b), as well as deficits in social and cognitive memory (Joushi et al., 2021). Future mechanistic work is needed to determine if this intervention also ameliorates the increase in drug abuse vulnerability induced by maternal separation.

5.2. Social Isolation

Evidence from rats and mice indicates that animals housed individually during adolescence display increased drug abuse vulnerability compared to group-housed controls. When tested in adulthood, social isolates show increased cocaine CPP (Zakharova et al., 2009), as well as increased SA of stimulants (Bardo et al., 2001; Ding et al., 2005; Schenk et al., 1987) and alcohol (Fernández et al., 2019; McCool and Chappell, 2009; Skelly et al., 2015). With cocaine or amphetamine SA, adolescent social isolation increases acquisition and escalation at low unit doses (Baarendse et al., 2013; Bardo et al., 2001; Boyle et al., 1991; Gipson et al., 2011; Howes et al., 2000; Schenk et al., 1987) and the effect is observed in both males and females (Bardo et al., 2001). While there have been some negative findings (Phillips et al., 1994; Rivera-Irizarry et al., 2020), several comprehensive reviews have concluded that most studies show *increased* drug SA following social isolation in adolescence, especially with stimulants and alcohol (Bardo et al., 2013; Vannan et al., 2018; Walker et al., 2019). Further, when enriching objects are introduced into the group-caged home environment, the difference between single- vs. group-housed rats is enhanced even further (Bardo et al., 2001; Stairs and Bardo, 2009), indicating that the combination of social peers and novel objects promotes greater protection against drug abuse compared to social peers alone. It is likely that social interactions in the presence of enriching objects are more complex than social interactions with peers alone because the presence of novel objects provides

opportunities for hiding and naturalistic territorial behaviors that promote full maturation of species-specific social competencies.

In contrast to stimulants and alcohol, relatively less is known about the effects of adolescent social isolation on opioid reward. One study found that social isolation decreases CPP induced by s.c. morphine (Wongwitdecha and Marsden, 1996), while another found no effect on SA assessed via the oral route (Hill and Powell, 1976). In contrast, using more clinically relevant routes of administration, adolescent social isolation has been shown to increase intranasal sufentanil SA (Weinhold et al., 1993) and acquisition of i.v. remifentanil SA (Hofford et al., 2017). Thus, similar to alcohol and stimulants, evidence indicates that adolescent social isolation enhances opioid abuse vulnerability when assessed using routes of administration with rapid absorption.

In addition to the increase in drug reward with social isolation, there is a concomitant strengthening of CRF systems and weakening of OT systems as described previously (Table 4), suggesting a role for these neuropeptides in linking social isolation and drug abuse vulnerability. However, as with maternal separation, caution is needed because these behavioral and neurochemical outcome measures have been typically observed in different studies, with relatively few studies measuring both drug reward and CRF or OT systems in the same animals.

While there have been no mechanistic studies directly examining the role of CRF or OT in linking social isolation and drug reward, some relevant studies have been conducted. In one study, microinjection of a CRF receptor antagonist into DR was shown to ameliorate the anxiety-like effect induced by adolescent social isolation (Lukkes et al., 2009a). Another study found that intra-DR microinjection of a CRF2 receptor antagonist ameliorated the social isolation-induced increase in anxiety (Bledsoe et al., 2011). Further mechanistic work is needed to determine if direct inhibition of CRF activity or excitation of OT activity also ameliorates drug abuse-related behaviors following adolescent social isolation.

5.3. Social Defeat

Acute and repeated social defeat applied during adulthood has an immediate and long-lasting impact on drug abuse vulnerability, which has been demonstrated most robustly with cocaine and alcohol reward (Montagud-Romero et al., 2018; Newman et al., 2018). Much of this work in adults has strongly implicated CRF as a key mediator of the relation between social defeat and increased drug intake. Like adults, adolescents exposed to social defeat and subsequently tested in adulthood show increased CPP to amphetamine, cocaine, and alcohol (Burke et al., 2011; Montagud-Romero et al., 2017; Rodríguez-Arias et al., 2017; Whitaker et al., 2013), as well as increased SA of cocaine and alcohol (Burke and Miczek, 2015; Rodriguez-Arias et al., 2016). Despite this evidence, there is relatively little known about the specific role of CRF in mediating the effect of adolescent social defeat on drug abuse vulnerability in adulthood. One recent review compiled 20 articles that applied social defeat during the adolescent period in mice and rats (McCormick et al., 2017). Among these, 3 studies examined plasma CORT and/or ACTH in adulthood (Burke et al., 2010; Buwalda et al., 2013; Furuta et al., 2015), but none examined these peripheral markers in conjunction with drug reward. One study found that the elevation in plasma CORT elicited by

experimenter-delivered amphetamine is reduced by adolescent social defeat (Burke et al., 2010) and another study found that peripheral administration of a CRF1 receptor antagonist attenuates the anhedonia associated with adolescent social defeat (Bourke et al., 2014).

A specific role of CRF systems in mediating the increase in drug reward with adolescent social defeat has been cogently advanced by others (Burke and Miczek, 2013), and is supported by literature cited in this review. Defeated rats display increased basal activity of noradrenergic neurons in LC, which is reversed by microinjection of a CRF1 antagonist into this same region (Bingham et al., 2011). Even more relevant, intra-VTA infusion of a CRF1 receptor antagonist during adolescent social defeat prevents the defeat-induced escalation of cocaine intake during adulthood (Burke et al., 2016). Similarly, while adolescent social defeat increases cocaine CPP in male mice, this effect is blunted by pretreating rats with a CRF1 receptor antagonist, but not a CRF2 receptor antagonist (Ferrer-Pérez et al., 2018). These mechanistic studies establish a direct role of CRF via activation of CRF1 receptors in mediating, at least in part, the relation between social defeat stress and drug abuse vulnerability.

There is also support for a mechanistic role of OT in mediating the relation between adolescent social defeat and drug reward. One recent study found that adolescent social defeat enhanced cocaine CPP in individually caged male mice, and that pair-housing with a familiar male or a female prevented the enhanced cocaine CPP and produced a concomitant elevation in plasma OT (Ferrer-Perez et al., 2019). In another study by this same group, pretreatment with an OT antagonist during the period of pair-housing, but not immediately prior to social defeat, abolished the protective effect of social housing on cocaine CPP (Ferrer-Pérez et al., 2020). Similarly, OT administration is able to ameliorate the increase in alcohol drinking normally induced by adolescent social defeat (Reguilón et al., 2021). These mechanistic studies indicate that the increase in drug abuse vulnerability induced by social defeat directly involves, at least in part, a weakening of OT systems and that the increased risk may be ameliorated with OT treatment.

5.4 Summary

Clear evidence indicates that early life adversity modelled by maternal separation, social isolation or social defeat increases drug abuse vulnerability across all drug classes, although the evidence is more robust with stimulants and alcohol compared to opioids. As described in the previous section (Section 4), these changes in behavioral risk are associated with a strengthening of CRF systems and weakening of OT systems. Several relevant mechanistic studies support a direct role of these neuropeptide systems in mediating the relation between drug abuse and early life adversity modelled by either maternal separation or social defeat. However, mechanistic studies are still needed to determine if these neuropeptide systems also link drug abuse and adolescent social isolation.

6. Conclusion

The overall theme presented here is that early life social adversity increases drug abuse vulnerability later in life because such adversity causes, at least in part, a strengthening of CRF systems and a weakening of OT systems. Consistent with this, ample evidence shows

that drug reward processing in adults is reduced by either CRF antagonists, particularly CRF1 receptor antagonists, or OT agonists. In addition, early life adversity modelled by maternal separation, adolescent social isolation or adolescent social defeat produces an increase in drug abuse vulnerability. The adversity-induced increase in risk is generally associated with a strengthening of CRF systems and a weakening of OT systems, although some negative findings are published. Importantly, although there are relatively few mechanistic studies conducted to date, they are consistent with the theme that the adversity-induced increase in drug reward (cocaine and alcohol) is directly related, as least in part, to increased CRF activity and decreased OT activity. However, with adolescent social isolation specifically, no published mechanistic studies have examined if the increase in drug abuse vulnerability is directly due to altered CRF and/or OT systems.

Conducting preclinical mechanistic studies to establish a direct role of CRF and OT systems in linking early life social adversity and drug abuse vulnerability could have translational value for treatment interventions in humans. Clinical work strongly implicates CRF and OT systems in the relation between early life trauma and drug abuse vulnerability (Fortunata Donadon et al., 2018; Kim et al., 2017), but critical proof-of-principle mechanistic studies are difficult to implement in human populations. Further, it is likely that there are interacting effects of CRF and OT following early life stress. For example, adult male smokers who experience early childhood adversity have elevated cortisol, an effect that is ameliorated by OT treatment (Hood et al., 2020). Thus, while substance use interventions that target CRF and OT systems hold great promise, additional preclinical and clinical studies are needed to determine how early life social adversity, combined with individual genetics, may be used to identify and target those at greatest risk.

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ABBREVIATIONS:

ACTH	adrenocorticotropic hormone
Amyg	amygdala
BNST	bed nucleus of the stria terminalis
BS	brainstem
CeA	central nucleus of the amygdala
CORT	corticosterone
CPP	conditioned place preference
CRF	corticotropin-releasing factor
CSF	cerebrospinal fluid
Ctx	cortex

DR	dorsal raphe
GABA	gamma-aminobutyric acid
Hipp	hippocampus
HPA	hypothalamic-pituitary-adrenal
Hypo	hypothalamus
i.c.v.	intracerebroventricular
i.p.	intraperitoneal
i.v.	intravenous
LC	locus coeruleus
LS	lateral septum
ME	median eminence
MFB	medial forebrain bundle
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid
MPOA	medial preoptic area
NAc	nucleus accumbens
OT	oxytocin
PAG	periaqueductal gray
PB	parabrachial nucleus
PFC	prefrontal cortex
Pit	pituitary
PND	postnatal day
PVN	paraventricular nucleus
RN	raphe nucleus
SA	self-administration
s.c.	subcutaneous
SC	spinal cord
Sep	septum
SON	supraoptic nucleus

STh	subthalamic nucleus
Str	striatum
Thal	thalamus
VMH	ventromedial hypothalamus
VTA	ventral tegmental area

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HIGHLIGHTS

- CRF and OT are involved in drug reward in adulthood.
- Early life social adversity strengthens CRF and weakens OT systems.
- Early life social adversity increases drug abuse vulnerability in adulthood.
- Changes in CRF and OT mediate the link between adversity and drug reward.
- Mechanistic studies of CRF and OT systems may be translated into clinical practice.

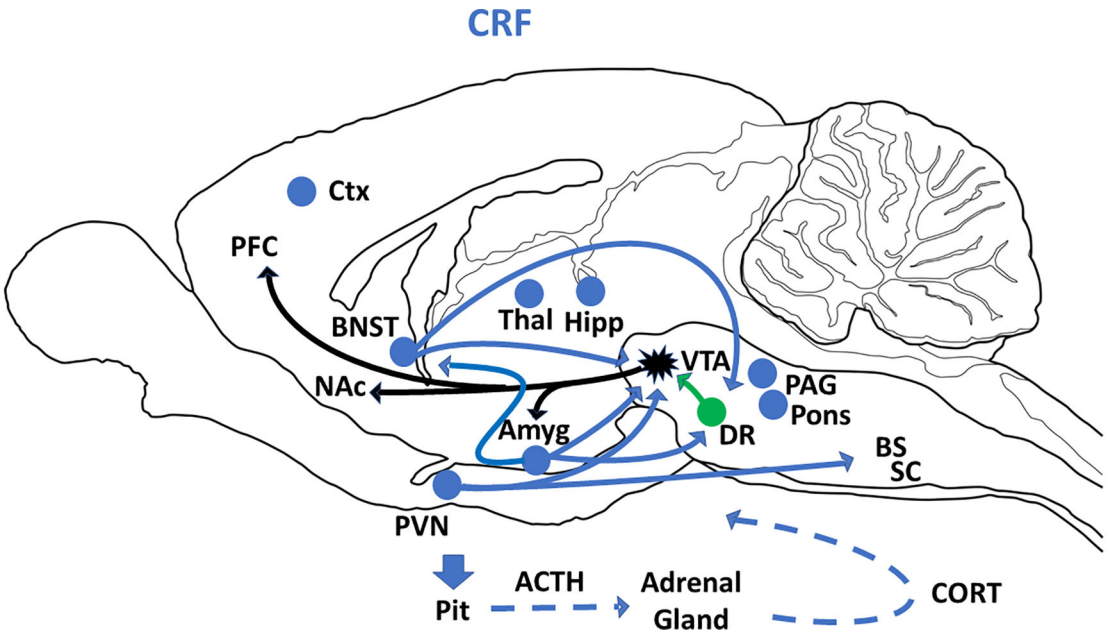

Figure 1:

Schematic summary of CRF cell bodies (blue circles) and CRF projections (blue arrows) in sagittal plane of rat brain. Blue circles without arrows identify possible additional efferents to VTA and blue dashed arrows represent blood circulation. The black projections from VTA represent dopamine neurons and green projections from DR represent serotonergic neurons. Adapted from the following references: (Forster et al., 2018; Kelly and Fudge, 2018; Kim et al., 2017). Abbreviations: ACTH=adrenocorticotropic hormone; Amyg=amygdala; BNST=bed nucleus of the stria terminalis; BS=brainstem; CORT=corticosterone; Ctx=cortex; DR=dorsal raphe; Hipp=hippocampus; NAc=nucleus accumbens; PAG=periaqueductal gray; PFC=prefrontal cortex; Pit=pituitary gland; PVN=paraventricular nucleus of hypothalamus; SC=spinal cord; Thal=thalamus; VTA=ventral tegmental area.

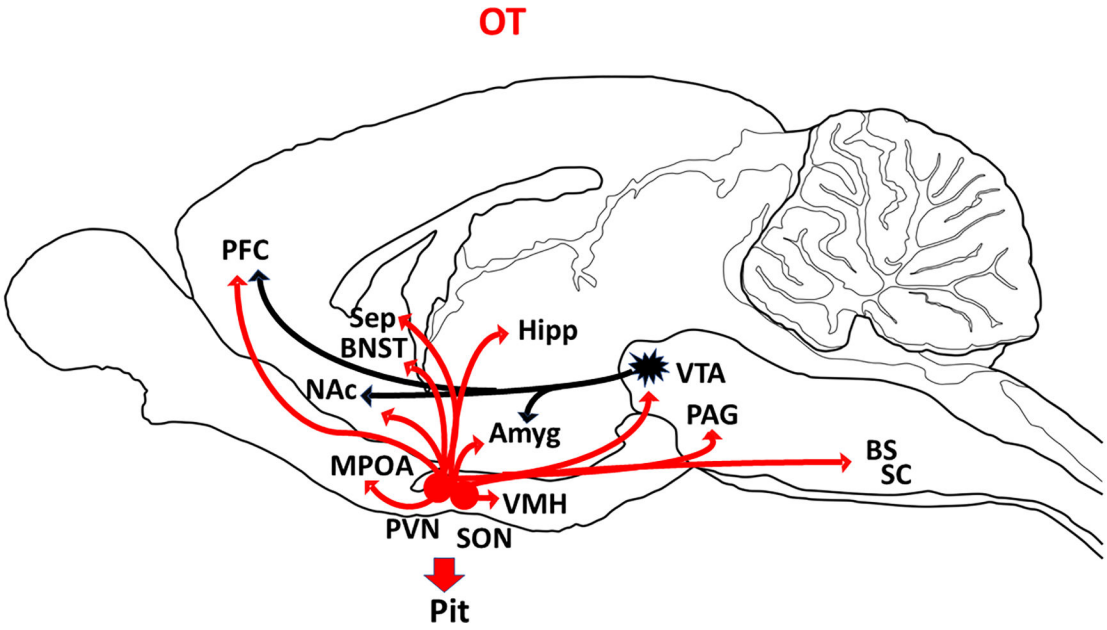

Figure 2:

Schematic summary of OT cell bodies (red circles) and OT projections (red arrows) in sagittal plane of rat brain. The black projections from VTA represent dopamine neurons. Adapted from the following references: (Baskerville and Douglas, 2010; Grinevich et al., 2016; Kim et al., 2017). Abbreviations: Amyg=amygdala; BNST=bed nucleus of the stria terminalis; BS=brainstem; Hipp=hippocampus; Sep=septum; MPOA=medial preoptic area; NAc=nucleus accumbens; PAG=periaqueductal gray; PFC=prefrontal cortex; Pit=pituitary gland; PVN=paraventricular nucleus of hypothalamus; SC=spinal cord; SON=supraoptic nucleus of hypothalamus; VMH=ventromedial hypothalamus; VTA=ventral tegmental area.

Table 1:

Summary of studies examining the effect of CRF agonists and antagonists on drug reward measured by either CPP or SA.

Reference	Species	Sex	Treatment	Route	Dose	Test	Result
Lemos et al., 2020	Sprague Dawley rats	Male	1) α-helical CRF 2) CRF	i.c.v.	1) 10 ug 2) 1 ug	CPP Cocaine (15 mg/kg)	1) ↓ acquisition 2) ↑ acquisition
Lu et al., 2003	Sprague-Dawley rats	Male	1) α-helical CRF 2) CP-154,526 (CRF1 antag) 3) AS-30 (CRF2 antag)	i.c.v.	1) 1 or 10 pg 2) 1 or 3 pg 3) 1 or 3 pg	CPP Cocaine (10 mg/kg)	1) ↓ acquisition 2) ↓ acquisition 3) ↔ acquisition
Specio et al., 2008	Wister rats	Male	1) Antalarmin (CRF1 antag) 2) MPZP (CRF1 antag)	1) ip. 2) s.c.	1) 6–25 mg/kg 2) 3–27 mg/kg	SA Cocaine (0.6 mg/kg/inf) 1- or 6-hr sessions	1) ↔ intake 1-hr ↓ intake 6-hr 2) ↓ intake 1-hr ↓ intake 6-hr
Mello et al., 2006	Rhesus monkeys	Female and male	Antalarmin (CRF1 antag)	i.v.	1–10 mg/kg	SA Cocaine (0.001–0.1 mg/kg/inf)	↔ intake
Przegalinski et al., 2005	Wistar rats	Male	CP 154,526 (CRF1 antag)	ip.	10–20 mg/kg	SA Cocaine (0.5 mg/kg)	↔ intake
Broadbear et al., 1999	Rhesus monkeys	Male	Astressin (CRF1 antag)	i.v.	0.1–1.0 mg/kg	SA Cocaine (0.03 mg/kg/inf)	↔ intake
Goeders and Guerin, 2000	Wistar rats	Male	CP 154,526 (CRF1 antag)	ip.	10–40 mg/kg	SA Cocaine (0.125–0.5 mg/kg/inf)	↓ intake ↔ food intake
Lasheras et al., 2014	Swiss mice	Male	CP 154,526 (CRF1 antag)	ip.	30 mg/kg	CPP Morphine (6 mg/kg)	↓ acquisition
Park et al., 2015	Wistar rats	Male	MPZP (CRF1 antag)	s.c.	20 mg/kg	SA Heroin (0.06 mg/kg/infusion)	↓ intake (escalation)
Greenwell et al., 2009	Wistar rats	Male	1) MJL-1–109-2 (CRF1 antag) 2) R121919 (CRF1 antag)	1) ip. 2) s.c.	1) 1.25–10 mg/kg 2) 5–20 mg/kg	SA Heroin (0.06 mg/kg/inf) 1) 1- or 8-hr sessions 2) 1- or 12-hr sessions	1) ↓ first-hr intake in 8-hr group 2) ↓ first-hr and total intake 12-hr group
Robinson et al., 2019	C57Bl/6J mice	Female and male	1) Antalarmin 2) NBI 35965 (CRF1 antag) 3) Ucn3 (CRF2 agonist) 4) K41498 (CrF 2 antag)	Intra-mPFC	1) 1 ug 2) 30 pmol 3) 60 pmol 4) 50 pmol	SA Alcohol (20 %) drink in dark	1) ↓ intake 2) ↓ intake 3) ↓ intake 4) ↔ intake 2)+4) combination reduces effect of 2) alone
Giardino and Ryabinin, 2013	C57BL/6J mice	Male	1) CP376395 (CRF1 antag) 2) NBI27914 (CRF1 antag)	ip.	1) 10 or 20 mg/kg 2) 10 or 30 mg/kg	SA Alcohol (15%) 2-bottle choice w/ drink in dark	1) ↓ intake 2) ↓ intake
Hwa et al., 2013	C57BL/6J mice and Long Evans rats	Male	CP 154,526 (CRF1 antag)	1) Intra-VTA 2) intra-DR	0.3 and 0.6 pg	SA Alcohol (20%) Intermittent 2-bottle choice	1) ↓ intake 2) ↓ intake, except low preferring rats

Reference	Species	Sex	Treatment	Route	Dose	Test	Result
Lowery et al., 2010	C57BL/6J mice	Male	1) α-helical CRF (non selective CRF antag) 2) Ucn3 (CrF 2 agonist) 3) CP 154, 526 (CRF1 antag)	1) i.c.v 2) i.c.v. 3) ip.	1) 1–10 μg 2) 0.05–0.5 μg 3) 1–10 mg/kg	SA alcohol (20 %) drink in dark	1) ↓ intake (1 pg only) 2) ↓ intake 3) ↓ intake, also w/adrenalectomy

Abbreviations: CPP=conditioned place preference; CRF=corticotropin-releasing factor; i.c.v.=intracerebroventricular; i.p.=intraperitoneal; i.v.=intravenous; mPFC=medial prefrontal cortex; SA=self-administration; s.c.=subcutaneous.

Table 2:

Summary of studies examining the effect of OT agonists and antagonists on drug reward measured by either CPP or SA.

Ref	Species	Sex	Treatment	Route	Dose	Measure	Result
Leong et al., 2016	Sprague Dawley rats	Female	OT	i.p.	0.1–3 mg/kg	SA Cocaine (0.15 mg/inf)	↓ intake
Baracz et al., 2012	Sprague Dawley rats	Male	OT	1) i.p. 2) intra-NAc 3) intra-STh	1) 0.6 mg/kg 2) 0.6 ng 3) 0.6 ng	CPP Methamphetamine (1 mg/kg)	1) ↓ acquisition 2) ↓ acquisition 3) ↓ acquisition
Qi et al., 2009	Swiss mice	Male	1) OT alone 2) OT+ atosiban (OT antag)	1) i.c.v. 2) i.c.v + i.c.v.	1) 0.1–2.5 μg 2) 2.5 μg + 2 μg	CPP Methamphetamine (2 mg/kg)	1) ↓ acquisition ↔expression 2) ↓ OT effect on acquisition
Cox et al., 2017	Sprague Dawley rats	Male and female	1) OT 2) OT 3) OT + OXA (OT antag)	1) intra-NAc 2) i.p. 3) i.p. + intra-NAc	1) 0.6 ug 2) 1 mg/kg 3) 1 mg/kg + 2 μg	SA Methamphetamine (17.5 or 20 μg/inf) economic demand	1) ↑ elasticity (α) 2) ↑ elasticity (α) 3) ↓ OT effect on elasticity
Cox et al., 2013	Long Evans rats	Male and female	OT	i.p.	0.3 or 1 mg/kg	SA Methamphetamine (17.5 or 20 μg/inf)	↓ PR breakpoint (females only)
Carson et al., 2010	Sprague Dawley rats	Male	OT	i.p.	0.001–1 mg/kg	SA Methamphetamine (0.1 mg/kg/inf)	↓intake
Lee et al., 2019	Sprague Dawley rat	Male	OT	i.p.	0.1–2 mg/kg	SA Methylphenidate (0.01–0.1 mg/kg/inf)	↓intake
Moaddab et al., 2015	Wistar rats	Male	1) OT 2) OTA (OT antag) 3) OT 4) OT + OTA	1) i.c.v. 2) i.c.v. 3) intra-NAc 3) intra-NAc	1) 0.2 2) 0.75 μg 3) 10 ng 2) 10 + 37.5 ng	CPP Morphine (5 mg/kg)	1) ↔ acquisition 2) ↔ acquisition 3) ↑ expression 4) ↓ OT effect on expression
Ibragimov et al., 1987	Sprague Dawley rats	Male	1) OT 2) OT + ACME-OT (OT antag)	1) intra-NAc or intra-Hipp 2) intra-Hipp	1) 2 ng 2) 2 + 2 ng	SA Heroin (20 μg/inf) tolerance induced with IP injections	1) ↓intake 2) ↑intake
Kovács and Van Ree, 1985	Wistar rats	Male	1) OT 2) OT1–8 (fragment) 3) OT4–8 (fragment) 4) OT7–9 (fragment)	s.c.	1 μg	SA Heroin (30 μg/inf) tolerance induced with IP injections	1) ↓ intake 2) ↓ intake 3) ↓ intake 4) ↔ intake
Kovács et al., 1985	CFY rats	Male	OT	s.c.	0.05–5 Mg	SA Heroin (20 μg/inf) tolerance induced with IP injections	↓intake
Van Ree and de Wied, 1977	Wistar rats	Male	1) OT 2) tocinamide (OT frag) 3) PLG (OT frag)	s.c.	1) 1 μg 2) 1 μg 3) 1 μg	SA Heroin (31 μg/inf) only 2 days acq training	1) ↑ intake 2) ↔ intake 3) ↑ intake

Ref	Species	Sex	Treatment	Route	Dose	Measure	Result
Bahi, 2015	C56BL/6J mice	Male	carbetocin (OT analog)	ip.	6.4 mg/kg	CPP Alcohol (2 g/kg)	↓acquisition
Stevenson et al., 2017	Prairie voles	Male and female	OT	ip.	1–10 mg/kg	SA Alcohol (15%) 2 bottle choice	↓intake
Tunstall et al., 2019	Wistar rats	Male	1) OT 2) OT 3) OT 4) PF-06655075 (OT agonist) 5) OT + L-371,257 (peripheral OT antag)	1) ip. 2) intranasal 3) i.c.v. 4) i.c.v 5) intranasal + i.p.	1) 0.125–1 mg/kg 2) 0.25–1 mg/kg 3) 3–30 μg 4) 30 μg 5) 1 mg/kg + 5 mg/kg	SA Alcohol (10%) lever pressing w/ vapor exposure	1) ↓ intake 2) ↓ intake 3) ↓ intake 4) ↓ intake 5) ↔ OT effect
King et al., 2017	C57BL/6J mice	Male	1) OT 2) OT + L-368,899 (OT antag)	1) ip. 2) i.p. + i.p.	1) 0.3–10 mg/kg 2) 1 + 10 mg/kg	SA Alcohol (20%) drink in dark or Alcohol (12%) lever pressing	1) ↓ intake 2) ↓ OT effect
Peters et al., 2017	Wistar rats	Male	OT	i.c.v.	1 Mg	SA Alcohol (20%) 2 bottle choice	↓intake
MacFadyen et al., 2016	Sprague Dawley rats	Male	OT	ip.	0.05–0.5 mg/kg	SA Alcohol (10–15%) 3 bottle choice w/drink in dark or Alcohol (10% gel) lever pressing	↓intake

Abbreviations: CPP=conditioned place preference; Hipp=hippocampus; i.c.v.=intracerebroventricular; i.p.=intraperitoneal; mPFC=medial prefrontal cortex; NAc=nucleus accumbens; OT=oxytocin; SA=self-administration; s.c.=subcutaneous; STh=subthalamic nucleus.

Table 3:

Summary of studies examining the long-lasting effect of maternal separation on development of CRF and OT systems.

Reference	Species	Sex	Maternal Separation Duration	Maternal Separation Age	Measurement Age	Result
Babygirija et al., 2012	Sprague-Dawley rats	Male	3 hr/day	PND 2–14	>PND 56 (following restraint stress)	↑ CRF mRNA in PVN ↑ CRF neurons in PVN
Flagel et al., 2003	Sprague-Dawley rats	Female and male	10 min/day	Early (PND 2–8) Late (PND 8–14)	PND 70	↔ CRF mRNA in PVN and Amyg
Garcia-Gutiérrez etal., 2016	Swiss ICR mice	Male	12 hr/day	PND 8 and 12	PND 28	↑ CRF mRNA in PVN
de Almeida Magalhães et al., 2018	C57BL/6 mice	Female and male	6 hr/day	PND 5–21	PND 45	↔ CRF mRNA in Hypo ↑ CRF1 and CRF2 receptor mRNA in Hipp
Slotten et al., 2006	Long-Evans rats	Male	3 hr/day	PND 3–15	PND 115–120	↔ CRF mRNA in PVN
Desbonnet et al., 2008	Wistar rats	Female and male	3 hr/day	PND 2–14	Adulthood (stressed vs. control)	↑ CRF neurons in PVN (stressed females only) ↓ CRF neurons in Amyg (males only)
Wang et al., 2014	Sprague-Dawley rats	Female and male	3 hr/day	PND 1–10	PND 77	↑ CRF mRNA in Hipp ↑ CRF protein in Hipp
Murgatroyd et al., 2009	C57BL/6N mice	Male	3 hr/day	PND 1–10	PND 90	↔ CRF mRNA in Hypo
Plotsky et al., 2005	Long-Evans rats	Female and male	Short 15 min/day Long 3 hr/day	PND 2–14	PND 100–120	↑ CRF in CSF (MS Long only) ↑ CRF mRNA and protein in PVN, Amyg, BNST and LC (MS Long only) ↑ CRF total receptor binding in PVN and LC (MS Long only) ↓ CRF total receptor binding in PVN and LC (MS Short only) ↑ CRF1 receptor binding and mRNA in PVN and LC (MS Long only) ↓ CRF1 receptor binding and mRNA in Ctx (MS Long only)
Aisa et al., 2008	Wistar rats	Females	3 hr/day	PND 2–21	PND 60–75	↑ CRF mRNA in PVN
O'Malley et al., 2011	Sprague-Dawley rats	Male	3 hr/day	PND 2–21	Adulthood	↑ CRF1 protein in Hypo ↔ CRF1 protein in PFC, Amyg or Hipp ↔ CRF2 protein in Hypo, Amyg or Hipp
Ladd et al., 1996	Sprague-Dawley rats	Male	4–6 hr/day	PND 2–20	PND 114–115	↓ CRF receptor binding in Pit ↑ CRF receptor binding in RN. ↑ CRF in ME, PB and RN
Plotsky and Meaney, 1993	Long-Evans rats	Female and male	3 hr/day	PND 2–14	PND 90–120	↑ CRF mRNA and content in Hypo
Chen et al., 2012	Sprague-Dawley rats	Female and male	4 hr/day	PND 2–13	PND 60	↑ CRF mRNA in Hypo (females only) ↔ CRF mRNA in Amyg

Reference	Species	Sex	Maternal Separation Duration	Maternal Separation Age	Measurement Age	Result
Bravo et al., 2011	Sprague-Dawley rats	Female and male	3 hr/day	PND 2–14	PND 77–91	↑ CRF1 mRNA in Amyg and RN ↔ CRF1 mRNA in Hipp ↓ CRF2 mRNA in Hipp, Amyg and RN
Hu et al., 2020	C57BL/6J	Male	24 hr	PND 3	PND 70–84	↑ CRF neurons in BNST ↑ CRF mRNA in BNST ↑ CRF1 receptor mRNA in BNST ↔ CRF2 receptor mRNA in BNST
He et al., 2018	Mandarin voles	Female	15 min/day	PND 1–14	Adulthood	↔ OT cells in PVN and SON
Gilles and Poston, 2017	Sprague-Dawley rats	Female and male	4 hr/day	PND 2–21	PND 103–107	↔ OT cells in PVN and SON
Riveros-Barrera and Duenas, 2016	Wistar rats	Female and male	3 hr/day	PND 1–21	1) PND 35 2) PND 90	1) ↔ OT in plasma 2) ↑ OT in plasma (females) ↓ OT in plasma (males)
Babygirija et al., 2012	Sprague-Dawley rats	Male	3 hr/day	PND 2–14	>PND 56 (following restraint stress)	↓ OT mRNA in PVN ↓ OT magno cells in PVN ↔ OT parvo cells in PVN
Tsuda et al., 2011	C57BL/6J mice	Male	3 hr/day	PND 1–14	PND 28–42	↑ OT cells in PVN
Barrett et al., 2015	Prairie voles	Female	3 hr/day	PND 1–14	PND 98	↔ OT receptors
Wei et al., 2020	Sprague-Dawley rats	Male	4 hr/day	PND 1–20	PND 42	↓ OT receptor mRNA in PFC ↓ OT receptor protein in PFC
Holubová et al., 2019	Wistar rats	Female and male	3 hr/day	PND 1–21	PND 30	↓ OT in plasma
Lukas et al., 2010	Wistar rats	Male	3 hr/day	PND 1–14	1) PND 35 2) PND 56 3) PND 112	1) ↓ OT receptors in Ctx 2) ↓ OT receptors in Ctx 3) ↓ OT receptors in Sep and Str ↑ OT receptors in VMH
Veenema et al., 2007	C57BL/6 mice	Female and male	3 hr/day	PND 1–14	>PND 98	↓ OT parvo cells in PVN (females only) ↔ OT magno cells in PVN
Oreland et al., 2010	Wistar rats	Male	Short 15 min/day Long 6 hr/day	PND 1–21	1) PND 21 2) PND 70	1) ↓ OT in Hypo (MS Short only) ↓ OT in Amyg ↑ OT in Pit (MS Short only) 2) ↔ OT in Hypo and Pit ↓ OT Amyg (MS Short only)
Melchior et al., 2018	Wistar rats	Female and male	3 hr/day	PND 2–12	PND 56	↔ OT receptor mRNA in SC

Abbreviations: Amyg=amydala; BNST=bed nucleus of the stria terminalis; CRF=corticotropin-releasing hormone; CSF=cerebrospinal fluid; Ctx=cortex; Hipp=hippocampus; Hypo=hypothalamus; LC=locus coeruleus; ME=median eminence; mRNA=messenger ribonucleic acid; OT=oxytocin; PB=parabrachial nucleus; PFC=prefrontal cortex; Pit=pituitary; PND=postnatal day; PVN=paraventricular nucleus; RN=raphe nucleus; SC=spinal cord; Sep=septum; SON=supraoptic nucleus; Str=striatum; VMH=ventromedial hypothalamus

Table 4:

Summary of studies examining the effect of adolescent social isolation on development of CRF and OT systems.

Reference	Species	Sex	Isolation Treatment	Isolation Age	Assessment Age	Result
Lukkes et al., 2009c	Sprague-Dawley rats	Male	1 vs 3 per cage	PND 21–42	PND 56	↔ CRF1 receptor protein in RN ↑ CRF2 receptor protein in dorsal RN
Pan et al., 2009	Prairie voles	Male	1 vs 2 per cage	PND 21–63	PND 66	↑ CRF in PVN ↔ CRF in Amyg
Weintraub et al., 2010	Sprague-Dawley rats	Female and male	1 vs 3 or 4 per cage	PND 30–50	PND 77	↔ CRF mRNA in parvocellular PVN
Ruscio et al., 2007	Prairie voles	Female and male	1 vs 2 (same or diff litter) per cage	PND 21–42	PND 42	↑ CRF in PVN ↔ CRF in Amyg
Pinelli et al., 2017	Sprague-Dawley rats	Female and male	1 vs 2 per cage	PND 35-140	PND 140	↔ CRF mRNA in Pit ↑ CRF1 receptor mRNA in Pit (male only) ↔ CRF2 receptor mRNA in Pit
Tanaka et al., 2010	Long-Evans rats	Female and male	1 vs 2 or 3 per cage	PND 23–37	PND 38–48	↓OT cells in PVN (females only)
Han et al., 2018	C57BL/6N mice	Male	single vs group cage	PND 42–77	PND 77	↔ OT mRNA in PVN ↓ OT receptor mRNA in Amyg
Pan et al., 2009	Prairie voles	Male	1 vs 2 per cage	PND 21–63	PND 66	↑ OT in PVN ↔ OT in SON
Pournajafi-Nazarloo et al., 2013	Prairie voles	Female and male	1 vs 2 per cage	PND 21–60	PND 60	↓ OT receptor mRNA in Hypo
Harvey et al., 2019	Sprague-Dawley rats	Female and male	1 vs 3 per cage	PND 21–77	PND 78	↓ OT in plasma
Ruscio et al., 2007	Prairie voles	Female and male	1 vs 2 (same or diff litter) per cage	PND 21–42	PND 42	↔ OT in PVN or SON
Oliveira et al., 2019	Wistar rats	Female and male	1 vs 3 or 4 per cage	PND 21–72	PND 74	↑ OT mRNA in PVN ↔ OT mRNA in SON ↓ OT receptor binding in NAc ↔ OT receptor binding in BNST, Sep, Amyg or VMH
Tanaka et al., 2019	Long-Evans rats	Female and male	1 vs 2 per cage	PND 23–87	PND 87–94	↔ OT cells in PVN or SON ↓ OT cells cFos+ in PVN and SON (female only)
Neal et al., 2018	Long-Evans rats	Male	1 vs 8 per cage	PND 29–55	>PND 55	↑ OT in plasma ↔ OT PVN, SON or MFB

Abbreviations: Amyg=amygdala; BNST=bed nucleus of the stria terminalis; CRF=corticotropin-releasing hormone; Hypo=hypothalamus; MFB=medial forebrain bundle; mRNA=messenger ribonucleic acid; NAc=nucleus accumbens; OT=oxytocin; Pit=pituitary; PND=postnatal day; PVN=paraventricular nucleus; RN=raphe nucleus; Sep=septum; SON=supraoptic nucleus; VMH=ventromedial hypothalamus.