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Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways

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Abstract

Substance addiction may follow a chronic, relapsing course and critically undermine the physical and psychological well-being of the affected individual and the social units of which the individual is a member. Despite the public health burden associated with substance addiction, treatment options remain suboptimal, with relapses often seen. The present review synthesizes growing insights from animal and human research to shed light upon developmental and neurobiological pathways that may increase susceptibility to addiction. We examine the dopamine system, the oxytocin system, and the glucocorticoid system, as they are particularly relevant to substance addiction. Our aim is to delineate how early adverse experience may induce long-lasting

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alterations in each of these systems at molecular, neuroendocrine, and behavioral levels and ultimately lead to heightened vulnerability to substance addiction. We further discuss how substance addiction in adulthood may increase the risk of suboptimal caregiving for the next generation, perpetuating the intergenerational cycle of early adverse experiences and addiction.

Keywords

early adverse experience; addiction; dopamine; oxytocin; glucocorticoid

Substance addiction continues to be a substantial and growing public health problem in the United States. According to the most recent national survey, 9.4% of the population used illicit drugs within the prior month.[1] The annual public health burden associated with tobacco, alcohol, and illicit drug use is estimated to be half a trillion dollars, including indirect costs to society.[2–4] Treatment options are often limited and suboptimal, and relapses are frequent. Substance addiction in mothers is particularly problematic, given the long-term negative impacts that addiction-related impairments in parenting and exposure to abused substances may have on children. Almost 90% of substance-using women are of reproductive age,[5] and an estimated 212,000 pregnancies annually involve illicit drugs, 370,000 involve alcohol, and 606,000 involve tobacco.[1] While many women abstain from substance use during pregnancy, many rapidly resume use after childbirth,[6] with resultant adverse effects on parenting capacity and child development. Substance use increases the odds of child neglect fourfold[7] and is a critical factor involved in a large majority of child maltreatment cases and infant out-of-home placements.[7–9]

The pathways leading to addiction are complex and multidimensional, and include differences in molecular and genetic expression, altered brain sensitivities to reward- and stress-related cues, and behavioral patterns that include risk taking, social isolation, and/or stress dysregulation (Fig. 1). Epidemiological studies have linked adverse childhood experience to addiction in adulthood,[10,11] with increased risk and severity related to greater frequency and duration of adversities experienced. Animal models have helped to elucidate developmental pathways by which early-life stress may affect neurobiological development and translate into behavioral patterns that increase susceptibility to addiction. In particular, three distinct but interrelated neurobiological systems are modified by early experience and patterns of maternal caregiving: (1) the dopamine (DA) system, (2) the oxytocin (OT) system, and (3) the glucocorticoid (GC) system. These three systems undergo substantial neurogenesis, apoptosis, and reorganization during early postnatal life, creating a window of potential adaptation and vulnerability to environmental influences.[12–16] Through epigenetic mechanisms, early-life experience appears to modify neuronal morphology, synaptic plasticity, and gene and receptor expression in each of these three systems, leading to changes in neuroendocrine functioning, neural circuit activation, and adult behavior, including substance-seeking behavior and addiction (Fig. 1).

Before proceeding, two clarifications are in order to frame this review. First, we use the term “early adverse experience” to refer to those experiences within the developing organism’s early environment, particularly maternal environment, that may compromise the offspring’s

developmental trajectory. By promoting homeostasis in the presence of internal and external stressors, the maternal environment is a major source of sensory stimulation critical for the organization of the brain network and the regulation of early physiology and behavior.[17,18] We therefore deem the early environment to be adverse when the mother's provision of sensory input is insufficient to promote optimal development (as in the case of maternal deprivation or neglect) or when her behavior induces excessive stress in the offspring rather than restoring homeostasis (as in the case of maternal abuse or rejection). While we include both under the same term of "early adversity," our intention is neither to imply that the nature of the two are identical nor to overlook the differences in their sequelae. Rather, we understand that both early deprivation and early stress, and the complex interplay between the two, constitute unique mechanisms by which early-life experience may induce long-term phenotypic alterations in the offspring.[19] With this in mind, we encompass in this review the literature ranging from early deprivation (e.g., maternal separation in rodents, maternal neglect in humans) to early abuse (e.g., maternal rejection in primates, maternal abuse of infants), as well as more subtle natural variations in maternal care (e.g., variations in licking and grooming in rodents, attachment in humans).

Second, we do not intend the present review to be exhaustive, either for the types of developmental experiences that may alter long-term trajectories or for the neurobiological mechanisms that may mediate such alterations. Although this review traces developmental trajectories starting from postnatal experiences, early deprivation or stress does not solely determine long-term developmental outcomes. Instead, the nature of early experience is such that its effects cascade into subsequent developmental stages and indirectly shape the kinds of experiences to which the developing organism is later exposed.[20] For example, it has long been known that the effects of early deprivation persist into subsequent social play with peers, undermining yet another critical experience[21] and thus yielding cascading developmental effects. Adult outcomes examined in this review, then, should best be understood as reflecting complex interactions between experiences accrued throughout the life span, including formative early experiences. Similarly, while we present the DA, OT, and GC systems largely in parallel (Fig. 1), these systems do not act in isolation, but in concert with one another. Furthermore, we note that developmental effects described in this review interact with other neurobiological systems not addressed here in detail, including the norepinephrine (NE), serotonin (5-HT), and γ-aminobutyric acid (GABA) systems. Our aim in selectively reviewing the DA, OT, and GC systems in this paper is to home in on the three systems that have established links to addiction and early experience in order to propose a developmental and intergenerational framework for addiction, which has thus far lacked such perspective in its conceptualization and treatment.

In what follows, we draw from both animal and human research to shed light upon how early adverse experience may modify the development of the DA, OT, and GC systems at the molecular, neuroendocrine, and behavioral levels. We examine long-term alterations observed in each of these three systems and delineate the processes by which these modifications increase susceptibility to addiction. We discuss further neuroadaptation related to extended substance use and consider how substance addiction may contribute to suboptimal early caregiving, thus increasing the likelihood of substance use in the next generation.

Dopamine system

DA is a catecholaminergic neurotransmitter that plays a pivotal role in the regulation of reward, motivation, and movement. The majority of DA neurons are located in the ventral part of the midbrain,[22] where the mesolimbic, mesocortical, and nigrostriatal DA systems originate (Fig. 2). The mesocorticolimbic DA system, known for its roles in reward and motivation, arises from the ventral tegmental area (VTA), with the mesolimbic pathway projecting to the ventral striatum (VS) and amygdala (AMY), and the mesocortical pathway projecting to the prefrontal cortex (PFC). The nigrostriatal DA system, responsible for regulation of voluntary movement and habit formation, originates from the substantia nigra (SN) and innervates the dorsolateral striatum. Given the important regulatory functions of DA, it is no surprise that DA-related dysfunctions are involved in the pathophysiology of major neuropsychiatric disorders, including substance addiction. The link between addiction and aberrant DA functions has been well established.[23,24] Growing attention is now increasingly directed to the role of early-life experience in shaping the development of the DA system. Below, we examine the links between early adverse experience, DA function, and susceptibility to addiction.

Molecular level

Animal models have shown that early adverse experience induces alterations in DA neuronal activity and synaptic function. Rodent studies have often employed a prolonged single episode (24 h) of maternal deprivation or periodic brief episodes (3–6 h) of maternal separation within the first 2 postnatal weeks to examine effects of early-life stress. Both paradigms are sufficient to alter the number of DA neuronal and glial cells, affect the rate of cell proliferation and apoptosis, and promote aberrant DA signaling in the VTA and SN in rodents.[25–27] Such dysregulation at least partly involves epigenetic modifications altering neuronal and synaptic plasticity,[25] which likely mediate long-term changes in the expression and function of DA neurons, receptors, and transporters observed in the key DA-innervated brain regions, including the striatum (STR) and PFC.[28,29] The direction of these changes observed to date has been mixed, with both hypo- and hyperactivity of the DA system reported. While the complex nature of these divergent findings merits further attention, the existing evidence suggests that early adversity may modulate the maturation of different DA circuits in a disparate manner (e.g., may induce DA release in the VS while blunting release in the PFC) and that seemingly equivocal findings may at least partly reflect differential levels of maturation and functioning of DA circuits involved at the time of adversity.[30]

Another line of rodent work has involved the study of naturally occurring variations in maternal behavior (i.e., licking/grooming in rats[a]). These studies have demonstrated that the quality of maternal care received early in life programs the development of the mesolimbic

[a]As we examine long-term developmental consequences of early-life experiences, we draw from growing data on natural within-species variations seen in rodent mothers' pup licking/grooming behaviors[55] as well as those observed in human mothers' infant-directed behaviors.[207] Low pup licking/grooming and compromised infant-directed caregiving behaviors are often regarded as negative, largely due to their links to long-term offspring outcomes that are generally considered adverse (such as those examined in this review, including high risk taking, social impairment, and high stress reactivity). However, we note here that developmental changes incurred by these early experiences have adaptive significance in their particular contexts and cannot simply be deemed as "good" or "bad."[19] Developmental adaptations tend to occur in such a way as to enhance a developing organism's chances of survival and functioning in the prevailing environment in which it exists. Inherent in this view is the understanding that adaptations to a given

DA system in the offspring. Rat pups exposed to high levels of postnatal maternal care display elevated density of DA cell bodies within the VTA and increased DA receptor mRNA levels within the VS,[31] much of which are understood to persist into adulthood.[31,32]

Neuroendocrine level

Altered basal DA levels have been detected in the STR and PFC of adolescent rodents exposed to early maternal separation.[33] Similar patterns have also been found in these animals in adulthood, with aberrant DA levels noted in the DA-innervated brain regions, including the VS[34] and AMY.[35] Notably, early adverse experience may also shift levels of stimulus-evoked DA release. Rodents with early adversity have been observed to display dampened DA release in the VS in response to pups,[34] enhanced DA release in the VS and hypothalamus (HYP) in response to stress,[35] and enhanced DA release in the VS in response to the administration of amphetamine.[36]

Although the study of the corresponding mechanisms in humans is comparably lagging, several positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have documented associations between early adverse experience and dysfunctions of the DA reward circuitry. In line with reports from rodent studies, suboptimal early caregiving has been linked to increased DA release in the VS in response to stress[37] and amphetamine administration.[38] Dampened reward-related VS and medial PFC activity have also been reported in mothers with suboptimal attachment in response to their own infant's smiling faces.[39] In a prospective fMRI study, early adversity measured at 3 months of age was associated with altered reward-related brain activity measured in adulthood in a dose-dependent manner.[40] As the number of exposures to adversity increased, reward-related brain activity increased during anticipation of monetary reward (in the VS and putamen) and decreased during receipt of reward (in the SN). Note that other groups examining the influences of adversity on neural responding have also documented decreased reward-related brain activity during receipt of reward,[39,41,42] suggesting that the direction of altered DA functions associated with early adversity may be mixed, in line with findings from rodent models.

Behavioral level

Behaviorally, rodents exposed to early maternal deprivation demonstrate heightened reactivity to novelty in adulthood, as reflected in their enhanced spontaneous locomotor activity in novel settings.[28,29] Novelty-seeking behavior predicts rodent sensitivity to rewarding properties of addictive substances and subsequent vulnerability to addictive behavior.[43,44] Indeed, rodents with early deprivation display heightened sensitivity to the effects of addictive substances, such as amphetamine[28,45] or cocaine.[29] They also learn to self-administer these substances faster and maintain longer bouts of self-administration.[46]

environment have trade-offs.[208] This is well reflected in findings from both animal models[209,210] and human studies,[211,212] suggesting that female offspring raised in an early environment characterized by low nurturance and safety (e.g., low licking/grooming in rodents, insecure mother–infant attachment in humans) often grow up to become adults who display low emotional stability (e.g., high stress reactivity, emotional health risks) but high reproductive success (e.g., early-onset puberty, increased sexual behavior, higher rate of pregnancy), whereas an early environment characterized by high nurturance and safety often leads to the opposite pattern.

In humans, novelty seeking, or sensation seeking, is defined as a trait characterized by a heightened tendency toward novel and intense sensations and experiences, often leading to impulsive risk taking and/or active pursuit of rewards.[47] The link between early adversity and novelty seeking has been established in both community[48] and high-risk samples.[49] Novelty seeking is positively correlated with a rise in DA release in the VS in response to amphetamine, as well as the individual's self-reported wanting of the drug.[50] Among different classes of substances, individuals with high novelty seeking display a preference for stimulant drugs that activate the DA pathway.[51] In a study of a large sample presenting with a complex set of risk factors, novelty seeking emerged as the strongest factor contributing to the development of substance-related disorders.[49] The link between childhood adversity and the presence of substance-related disorders was found to be at least partially mediated by increased novelty seeking in individuals with adverse histories.[49]

Oxytocin system

OT is a neuropeptide that functions as a key neuroregulator of social behavior across mammalian species.[52] OT is synthesized in the magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON) of the HYP and is transported to the posterior pituitary gland, where it is released into the periphery (Fig. 2).[53] Within the central nervous system, OT neurons project between brain regions known to be critical for the regulation of social behavior, including the medial preoptic area (MPOA) of the HYP, bed nucleus of the stria terminalis (BNST), VTA, VS, AMY, and lateral septum (LS).[54,55] The long-known functions of OT, including uterine contraction during labor and milk ejection during lactation, arise from the peptide's peripheral actions. Recently, considerable attention has surrounded OT's central actions, including its role in attachment formation and stress regulation. The past few decades have seen a surge of interest in the link between disorders of psychosocial functions and the dysregulated OT system.[56–58] This line of research is now being extended to the area of addiction.[59] The OT system is particularly germane to our discussion, given its unique susceptibility to undergo alteration via interaction with early environments. Growing evidence points to early experience as one of the most robust predictors of long-term OT functions. Below, we delineate the proposed links between early-life experience, OT functions, and vulnerability to addiction.

Molecular level

Rodent studies examining natural variations in maternal behavior have provided a fine-grained examination of how early environment shapes the long-term development of the OT system. Low levels of maternal care (i.e., licking/grooming in rats) experienced early in life are directly associated with the reduced density of OT receptors observed in the MPOA, PVN, BNST, AMY, and LS.[55,60–62] Importantly, cross-fostering studies suggest that these effects are not associated with genetic variation, but are rather a consequence of disrupted early attachment, operating through changes in epigenetic regulation occurring via altered DNA methylation.[63]

Experimentally induced early deprivation also produces persistent alterations in OT and OT receptor systems. Deprivation experienced during the first 2 weeks of rodent life suppresses

cell proliferation and reduces the number and size of cell bodies observed within the MPOA.[64] Comparable results have been reported in the PVN and SON of the HYP, where a stable reduction in the number of cells has been documented in response to early deprivation, a finding that was at least partly attributable to a decrease in the number of OT-producing neurons.[65–67] Early adversity also interferes with the normative age-dependent developmental adaptations within the OT receptor system. Maternal separation accelerates an age-related increase in OT receptor binding in the HYP, as well as age-related decreases in the STR and LS, contributing to abnormally high or low binding densities in adulthood, respectively.[68] These changes are often detected shortly following the experimental manipulation and persist into adulthood.[64,65]

Neuroendocrine level

Altered OT levels have been documented in rodents exposed to low levels of naturally occurring maternal care[69] or experimentally induced early separation.[70] These effects have been observed in specific OT-innervated brain regions, such as the HYP or AMY,[70,71] as well as in the plasma.[69] Observed changes are generally in the direction of blunted OT levels in those exposed to early adversity, although it has been proposed that prolonged exposure may lead to a rise in OT levels as a way of protecting the system from the deleterious effects of stress.[72,73] While studies involving primates are more sparse, rhesus monkeys reared in nurseries show reduced levels of cerebrospinal fluid (CSF) OT compared to those reared by their mothers,[74] paralleling results from rodent models.

In humans, a history of childhood trauma or stress is consistently negatively correlated with levels of OT measured in CSF, plasma, or urine.[75–78] These reports often reveal a dose-dependent inverse relationship between the number of trauma exposures and OT concentration.[52,54] Among different forms of trauma, emotional abuse and neglect appear to produce the strongest effects.[76,77] The timing of adversity also seems critical, given that adverse experiences in childhood, but not those in adolescence or adulthood, emerge as robust predictors of long-term disruptions in OT functions.[78] The effects of more subtle suboptimal attachment have also been examined. Infants or children who receive less synchronous, sensitive, or responsive caregiving show blunted salivary OT levels, both at baseline and in response to social cues.[79,80] Adults who retrospectively report such early histories similarly display blunting of OT in plasma or serum, both at baseline and in response to social cues.[39,81,82] A few fMRI studies have linked these blunted peripheral OT functions to the dysregulated activity of OT-innervated brain regions, including the HYP, VS, and AMY.[39,83,84] During processing of socially salient cues, suboptimal early history emerges as an important modulator of the activity of these brain regions,[39,85] dampening the reward salience of social cues (possibly via actions on the VS and VTA) while enhancing stress arousal (possibly via actions on the AMY).

Behavioral level

Behaviorally, rodents exposed to early-life deprivation show a wide array of social impairments. They display diminished social motivation,[66] reduced affiliative behavior,[71] impaired social learning,[86] and increased aggressive behavior.[66,67] Primates exposed to adverse rearing similarly show preference for solitary activity, while also demonstrating

reduced capacity to use social companionship in times of stress.[74] Natural variations in early rearing conditions may also directly shape the animal's long-term social functions. Rodents who receive low levels of care early in life tend to develop into adults who display similarly low levels of care to their own pups.[87,88] This intergenerational transmission appears to be partially mediated by the OT-related molecular and neuroendocrine alterations outlined above.[55,61,74]

Findings from human studies parallel those from animal models. Profound early deprivation, as was seen in Romanian institutional rearing, has been observed to lead to severe long-term attachment disturbances and social deficits.[89,90] The developmental literature is replete with decades of prospective longitudinal and cross-sectional studies linking early trauma and/or disrupted attachment to long-term social and attachment dysfunction.[91–94] There has been an increasing number of studies linking these social deficits to compromised OT functions.[57,95,96]

Recent advances in neuroscience have revealed that there may be a significant overlap in the neurobiological mechanisms that underpin social attachment and addiction.[97,98] In addiction, neural systems integral to the formation of social attachment may be co-opted for the maintenance of addictive behavior.[98] Consistently, social impairment often presents as a significant risk factor for the development of addiction. Social isolation in rodents has been linked to heightened vulnerability to the effects of addictive substances[99] and to subsequent addictive behavior.[100] In humans, low social support and high social isolation often precipitate the emergence and recurrence of substance use and are among the strongest predictors of substance addiction, above and beyond sociodemographic variables.[101]

This body of research is further complemented by reports demonstrating that centrally acting OT can inhibit the development of preferences for addictive substances,[102,103] facilitate the extinction of previously formed substance preferences,[103] reduce the self-administration of substances,[104] block the development of tolerance or withdrawal symptoms,[105] and prevent the reinstatement of substance-seeking behavior under conditions of stress.[103,106] These effects have been documented following intracerebroventricular or region-specific injections of OT in the VS, HYP, or medial PFC, and have been observed with regard to a wide range of addictive substances, including methamphetamine, heroin, cocaine, morphine, and opiates.[102–106] While corresponding studies in humans are scarce, initial reports demonstrated the potential utility of intranasally administered OT in attenuating symptoms of alcohol withdrawal[107] and cannabis craving.[108] However, the early optimism has been gradually tempered by reports suggesting that the therapeutic effects of OT are more nuanced than initially assumed.[57,109] Recently, OT administration was found to exacerbate symptoms of addiction in inpatients with cocaine dependence.[110] More systematic studies are needed to tease apart the promise of OT administration in the treatment of substance addiction.

Glucocorticoid system

GCs (cortisol in primates and corticosterone (CORT) in rodents) are a family of steroid hormones that coordinate an organism's physiological responses to stress. A cascading set of

neurotransmitters and hormones involved in this coordination is collectively known as the hypothalamus–pituitary–adrenal (HPA) axis (Fig. 2).[111] Physical or psychological stress activates the parvocellular neurons of the hypothalamic PVN to release corticotropin-releasing factor (CRF). CRF binds to receptors in the pituitary to stimulate adrenocorticotropic hormone (ACTH) production. ACTH is then transported to adrenal glands, culminating in the secretion of GCs. Once released, GCs act at glucocorticoid receptors (GRs) throughout the corticolimbic structures, including the HYP, pituitary, and hippocampus, to suppress further synthesis and release of CRF and ACTH, thereby attenuating the activity of the HPA system and restoring homeostasis (i.e., GC negative feedback).[112] The hippocampus contains high concentrations of GRs[113] and is a primary site in the negative regulation of the HPA axis.[114]

On the other hand, the AMY is the origin of major CRF pathways in the brain, is a primary extrahypothalamic source of CRF, and plays a critical role in mobilizing the activity of the HPA axis.[115] CRF neurons originating from the AMY project to the locus coeruleus (LC) and synapse onto catecholaminergic neurons, stimulating the release of NE.[115] Pronounced reciprocal interactions exist between the CRF and NE systems, whereby CRF enhances the release of NE and NE, in turn, stimulates the release of CRF. This CRF–NE interaction has been observed in the HYP, AMY, BNST, and LC and is understood to progressively augment stress responsivity in the face of repeated challenges to homeostasis.[116] The AMY also serves as a site of interaction between the HPA and the 5-HT and GABA systems. The AMY provides a major source of CRF innervation to the dorsal raphe nucleus (dRN),[115] where the 5-HT system originates. While our understanding of the nature and direction of 5-HT modulation remains incomplete,[117,118] CRF actions in the dRN modulate stress-induced 5-HT release in the AMY, which is pivotal to the regulation of the HPA axis activity.[119] GABA cells are found adjacent to CRF neurons in the AMY and inhibit the activity of CRF in the AMY and LC.[115] Given the effects of early-life adversity and HPA dysfunction on the etiology of stress-related disorders, the developmental programming of the GC stress system has received considerable study. Below, we examine links between early-life experience, GC functions, and vulnerability to addiction.

Molecular level

Variations in naturally occurring maternal care have been identified as a nongenomic mechanism programming the development of the rodent's GC functions. Low levels of early maternal care increase CRF mRNA expression in the hypothalamic PVN and decrease GR mRNA expression in the hippocampus.[120] These altered levels of gene expression are correlated with levels of maternal care observed during the first week of postnatal life[120] and may be at least partially mediated by the altered epigenome at a GR gene promoter in the hippocampus.[121] These effects emerge over the first week of the rodent's life, are reversed with cross-fostering, and persist into adulthood.[121] Low maternal care has also been found to lead to a reduced density of GABA and benzodiazepine receptors in the AMY and LC,[122,123] as well as increased CRF receptor and decreased adrenoreceptor densities in the LC.[122] Stable structural alterations have also been observed in the hippocampus, with decreases in neuronal survival,[124,125] dendritic complexity,[126] and synaptic density and plasticity[126,127] documented in rodents with a history of low maternal care.

Experimentally induced early deprivation similarly produces long-term abnormalities in the rodent's GC functions. Early maternal separation reduces the density of CRF receptors in the pituitary while increasing the densities in the HYP, AMY, dRN, and hippocampus.[128–130] The density of GRs in the hippocampus,[131] as well as those of GABA and benzodiazepine receptors in the AMY and LC,[132] has been found to decrease as a result of early adversity. Decreased 5-HT receptor mRNA expression has also been observed in the dRN of these rodents, while increased expression has been seen in the AMY.[133,134] Long-lasting morphological and functional changes are also found in the hippocampus following repeated maternal separations.[135] These rodents display a reduced density of hippocampal axons, decreased cell proliferation, and dysregulated neurogenesis in adulthood.[135,136]

Neuroendocrine level

Natural variations in maternal care are directly associated with individual variations seen in the reactivity of the HPA axis in the adult offspring. As adults, rodents who received low maternal care display significantly elevated stress-induced plasma ACTH and CORT levels,[120] the magnitude of which are inversely proportional to the frequency of maternal behavior (e.g., licking/grooming) observed early in life. These elevations may be mediated at least in part by impaired GC negative feedback on the HPA axis.[120,137] Experimentally induced maternal separation is documented to be sufficiently adverse to evoke a significant rise in the HPA-axis response,[135] resulting in exaggerated stress-induced ACTH and CORT responses during the first 2 postnatal weeks,[128] when rat pups are normally hyporesponsive to stressors. Later in life, these animals are observed to display increased basal hypothalamic CRF synthesis, enhanced stress-induced CRF release, elevated poststress plasma ACTH and CORT levels, and reduced sensitivity to GC negative feedback, demonstrating that these effects persist throughout their life span.[129,131,137]

Reports from nonhuman primates are generally in line with these findings and demonstrate persistently altered HPA functions in animals with a history of early adversity. Macaques or common marmosets exposed to early adversity display elevated CSF concentrations of CRF and NE,[138,139] decreased CSF concentrations of 5-HT metabolites,[139,140] and flattened diurnal rhythms of cortisol secretion (i.e., lower than normal morning cortisol levels).[141]. Cortisol levels are also altered in these animals, although the direction of the effect appears to be mixed.[138,142] It has been proposed that early-life stress may initially induce acute elevations in cortisol, but persistent elevations in the presence of repeated, prolonged stressors may over time lead to an adaptive blunting of ACTH response to CRF,[143] leading to lower than normal cortisol levels later in life.[142,144]

In humans, less synchronous, sensitive, and responsive early caregiving has been consistently associated with exaggerated or prolonged increase in cortisol in response to stress.[145,146] However, in cases of more severe early deprivation or maltreatment, patterns of HPA responsiveness thus far examined have been inconsistent.[111,144] Both elevated[147] and dampened[148] cortisol levels have been reported in these individuals, along with both increased[149] and blunted[150] stress-induced activation of brain regions, such as the AMY, involved in the regulation of HPA functions. While the mixed findings are understood to be at least in part due to the complex nature of maltreatment and the comorbidity of a range of

psychiatric disorders present at the time of the assessment, there is growing consensus that affected individuals may undergo a transition from early hypercortisolism to later hypocortisolism upon continued exposure to adversity.[144,151] This change may reflect the adaptive downregulation of the HPA system following chronic stress exposure, subsequently leading to flattened diurnal rhythms of cortisol secretion (lower than normal daytime cortisol levels),[152,153] consistent with reports from nonhuman primate models.

Behavioral level

These molecular and neuroendocrine alterations of the GC system diminish the animal's capacity to effectively respond to stress. Rodents who receive compromised early maternal care, whether naturally occurring or experimentally induced, display substantially increased fearfulness and anxiety in adulthood, along with decreased exploration and increased inhibition.[122,135,154] Nonhuman primates exposed to compromised rearing conditions display similar behavioral impairments, reflecting disturbances in stress reactivity.[141,155,156] These behavioral outcomes have been reported by many to resemble signs and symptoms of anxiety, depressive, and addictive disorders.[142,157,158]

In humans, early adverse experience is a potent risk factor for the development of depressive, anxiety, or trauma-related disorders later in life.[159–163] Altered GC functions and HPA responsiveness may play critical roles in the etiology of these disorders and have received attention as potentially important mediators linking early adversity and later psychopathology,[164,165] along with accompanying disruptions in NE, 5-HT, and GABA functions.[159,166] A wealth of data implicates stress dysregulation and HPA dysfunction in substance addiction.[98,166] Stress exposure can precipitate the onset of substance use, dampen the motivation to discontinue use, and enhance the risk for relapse, particularly in those who exhibit enhanced HPA reactivity.[166] This process may reflect the effects of a chronically activated HPA axis on enhanced striatal extracellular DA release, which may sensitize the reward system to the reinforcing properties of addictive substances.[37,167,168] Disorders that centrally implicate HPA dysfunctions, such as depressive, anxiety, and trauma-related disorders, can serve as precursors to the development of substance addiction.[164,165,169] These disorders also modulate the progression of substance addiction such that the illness course is typically more severe and persistent.[170]

Substance addiction: compounding dysfunctions

While long-term alterations in the DA, OT, and GC systems examined above increase one's susceptibility to addiction, the resulting substance addiction may lead to continued perturbations in each of these three systems. Repeated exposure to addictive substances may induce an aberrant surge of DA in the VTA and VS, which, over time, may lead to a series of neuroadaptations in the mesolimbic DA system at molecular, cellular, and neural levels.[171,172] Disrupted DA signaling and synaptic neurotransmission have been detected in the VTA and VS.[173,174] With extended substance use, the DA reward threshold may be recalibrated, with a shift within the reward system occurring in the direction of heightening the incentive salience of addictive substances while dampening that of natural reinforcers.[23]

While substance use initially evokes acute activation of the HPA axis, high circulating levels of GCs in the presence of continued substance use can blunt HPA activity while sensitizing the CRF and NE systems in the AMY.[175] With extended substance use, the normal circadian rhythm of GC secretion becomes blunted, such that a complete reversal of normal rhythm is observed.[176] As substance use persists and tolerance is developed, the HPA-axis activity progressively decreases, along with pituitary GR mRNA levels.[177] In contrast, a state of withdrawal is marked by increased hypothalamic CRF mRNA expression,[178] elevated extracellular levels of extrahypothalamic CRF and NE in the AMY and BNST,[179–182] and intensified HPA reactivity to stress,[178] mechanisms that are likely to contribute to continued substance seeking, sustained negative affect, and eventual relapse.

Long-lasting neuroadaptations have also been documented within the OT system. Increased degeneration is seen in the magnocellular OT neurons in the hypothalamic PVN with chronic substance exposure.[183,184] OT synthesis decreases in the MPOA and HYP over time,[185,186] and there is a downregulation of OT receptor expression and diminished OT innervation in the VS.[187] Sustained behavioral impairments reflect these ongoing disruptions at molecular and neuroendocrine levels. As addiction progresses, impulsivity and risk taking intensify, while social dysfunctions are exacerbated. Dysphoria, nervousness, and negative affect also become increasingly prevalent, dissipating upon exposure to addictive substances only to become stronger and harder to dispel with continued exposures.[23]

The DA, OT, and GC systems that have thus far been examined in parallel also interact with one another. DA and OT receptors colocalize in the PVN, SON, VS, AMY, and medial PFC,[188] allowing a close coordination between the two systems.[189] While the nature and direction of the interactions between the two systems appear to vary depending on the context,[190] OT is understood to inhibit DA stimulation in the context of substance exposure,[191] a mechanism that likely becomes attenuated with extended substance use. GCs also regulate mesolimbic DA transmission. Stress-induced GCs alter synaptic plasticity, receptor function, and dendritic organization in the VTA and VS in the direction of augmenting mesolimbic DA release.[192–194] While the effects of GCs grow stronger in the presence of heightened DA activity, the presence of GCs also heightens the reactivity of mesolimbic DA neurons to the reinforcing effects of addictive substances and increases the propensity that addiction will persist,[195] an effect at least partly mediated by CRF-induced cAMP response element–binding protein (CREB) phosphorylation.[196] As addiction progresses and the DA, OT, and GC systems respond to persistent challenges to homeostasis (i.e., substance exposure), the intricately regulated balance between the three systems continues to deviate from its normal homeostatic range.[23,98,175] The concept of allostasis has been used to explain the spiraling dysregulation and is characterized by a feedforward mechanism aimed at achieving apparent stability outside of the normal homeostatic range through continued adaptation to chronic demands.[175,197]

Substance addiction and beyond: intergenerational effects

Vast repercussions accompany the perturbations in the neurobiology and behavior summarized above. While documented consequences are wide ranging, impaired maternal care is particularly pertinent to the topic at hand,[198] given the pivotal role that maternal care

plays in shaping the early experience of the next generation. The transition to motherhood is supported by multiple neuroadaptations at molecular, cellular, and neuroendocrine levels, notably in the same three systems examined above—namely, the DA, OT, and GC systems.[98,199,200] As reviewed in the present paper, substance-using mothers may display increased vulnerability to dysregulated functions in each of these systems as compared to non-using mothers, potentially due to their own early histories or substance use, or both. Indeed, the DA, OT, and GC systems that are central to maternal caregiving are understood to be co-opted in maternal substance addiction,[98] which sensitizes each of these systems to the gratification and relief associated with substance use at the expense of dampening the salience of cues from their own infants.[23] Not surprisingly, decades of animal and human research underscore the link between substance addiction and impaired maternal caregiving, moderated by a variety of environmental and social factors that may strengthen or undermine the link. Substance-using mothers, compared to non-using mothers, are observed to be less attentive and responsive to their infants, while being more intrusive and hostile.[170] Both on behavioral and neural levels, they find infant cues to be less gratifying and more stressful,[98,201,202] which may place the infant at an increased risk for abuse or neglect.

Thus, it appears that parenting difficulties associated with addiction may increase the risk that the infant's early environment will be less than optimal. This can lead to the perpetuation of adverse childhood experiences, thereby continuing the cycle of early adversity and addiction.[10,203] There is a preponderance of evidence in support of this notion. The risk for abuse and neglect appears to rise substantially in the presence of substance addiction.[7] Infants of substance-using mothers are considerably more likely to be removed from their mothers and placed in out-of-home care.[8] Substance-using mothers also exhibit elevated levels of parenting stress, which can give rise to an increased display of problematic parenting behaviors.[204] Taken together, these findings point to a pattern of intergenerational effects, whereby mothers with substance addiction have often experienced inadequate caregiving environments during their own childhood, while their own substance use in adulthood increases the likelihood that they will provide neglectful or abusive care to their children.

Conclusions

The present paper reviewed the mechanisms by which early-life experience shapes the DA, OT, and GC systems in the developing brain. We have summarized long-lasting molecular, neuroendocrine, and behavioral alterations that occur in animals and humans following early-life adversity. We have examined these modifications with regard to their effects on substance addiction and have shown that these alterations may serve as mediating pathways between early adverse experience and enhanced susceptibility to addiction. We have further reviewed how substance addiction, once developed, may promote compromised parenting behavior, increasing the possibility that less-than-optimal care will be provided to the next generation. This is likely to lead to the perpetuation of early adversity and addiction in the generations that follow, unless appropriate prevention and intervention efforts are made.

Current treatment strategies for substance-use disorders tend to focus on the individual and the cessation of substance use, rather than the developmental and social processes that may

perpetuate addiction. A notable exception to this can be found in an attachment-based parenting intervention model for substance-using women, which targets the quality of relationships between substance-using mothers and their young children and has been shown to be effective in reducing substance use.[205,206] The developmental perspective underscored in the present review proposes an intergenerational conceptual framework linking addiction susceptibility to early adversity, chronic stress, and changes in the function and regulation of neurobiological systems. This perspective is innovative in implicitly proposing that addiction is a developmental disorder and that early adversity and chronic stress may be precursors for a number of later adult psychiatric disorders associated with disruptions in both social processes and the positive and negative valence systems. Such a developmental approach also shifts the focus in addiction treatment from an intervention to a prevention model and provides a novel way to consider how to break the cycle of addiction for the next generation.

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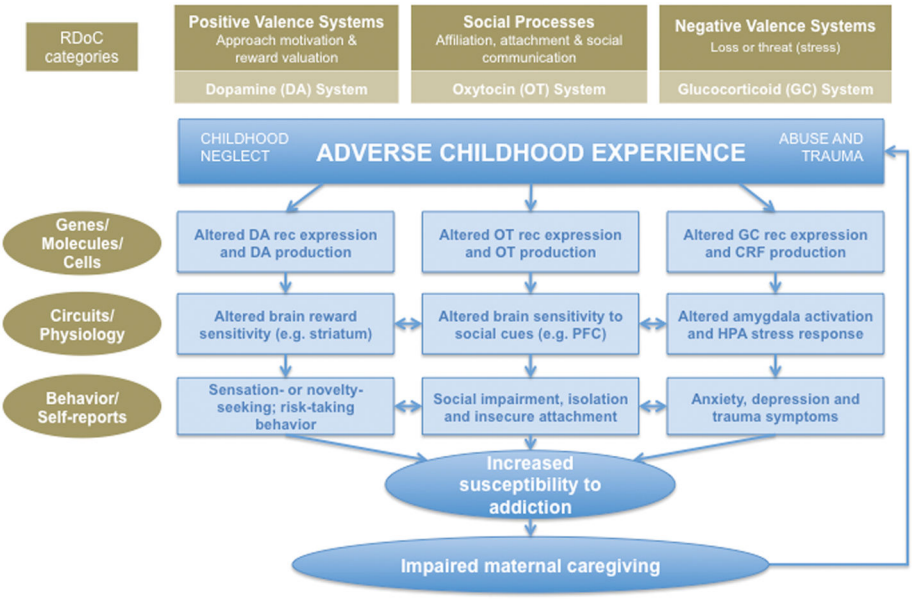

Figure 1.

Developmental and neurobiological pathways linking adverse childhood experience to susceptibility to addiction, via modifications in dopamine, oxytocin, and glucocorticoid systems at molecular, neuroendocrine, and behavioral levels. The model uses categories from the National Institute of Mental Health's Research Domain Criteria (RDoC). DA, dopamine; OT, oxytocin; GC, glucocorticoid; rec, receptor; CRF, corticotropin-releasing factor; PFC, prefrontal cortex

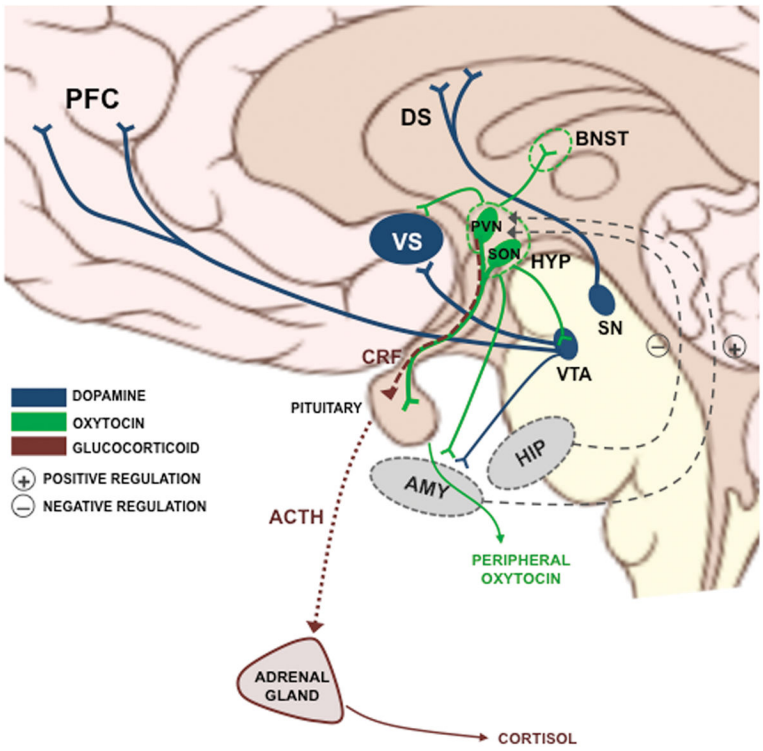

Figure 2.

Dopamine, oxytocin, and glucocorticoid systems of the human brain proposed to mediate the links between early adverse experience and substance addiction. Brain schematic by P. J. Lynch (2006; CC BY 2.5). VTA, ventral tegmental area; SN, substantia nigra; PVN, paraventricular nucleus; SON, supraoptic nucleus; HYP, hypothalamus; VS, ventral striatum; DS, dorsal striatum; BNST, bed nucleus of stria terminalis; PFC, prefrontal cortex; AMY, amygdala (not shown); HIP, hippocampus (not shown); CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone