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REVIEW

Potential programming of dopaminergic circuits by early life stress

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Abstract Stress and high levels of glucocorticoids during pre- and early postnatal life seem to alter developmental programs that assure dopaminergic transmission in the mesolimbic, mesocortical, and nigrostriatal systems. The induced changes are likely to be determined by the ontogenetic state of development of these brain regions at the time of stress exposure and their stability is associated with increased lifetime susceptibility to psychiatric disorders, including drug addiction. This article is intended to serve as a starting point for future studies aimed at the attenuation or reversal of the effects of adverse early life events on dopamine-regulated behaviors.

Keywords Programming · Glucocorticoids · Dopamine · Mesolimbic · Mesocortical · Nigrostriatal · Tuberoinfundibular · Addiction · Depression · Anxiety · Nucleus accumbens · Ventral tegmental area

Abbreviations

DA	Dopamine
DAergic	Dopaminergic
TH	Tyrosine hydroxylase
L-DOPA	Levodopa
ELS	Early life stress
ADHD	Attention deficit hyperactivity disorder
HPA	Hypothalamus–pituitary–adrenal axis
GC	Glucocorticoids
VTA	Ventral tegmental area
NAcc	Nucleus accumbens

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Introduction

The catecholaminergic neurotransmitter dopamine (DA; 4-[2-aminoethyl]benzene-1,2-diol) is prominently involved in a number of brain functions such as cognition, emotion, reward, and motor control (Nieoullon and Coquerel 2003; Wise 2008), as well as neuropsychiatric disorders such as schizophrenia, drug addiction, attention deficit hyperactivity disorder (ADHD), and Parkinson's disease (Genro et al. 2010; Howes and Kapur 2009; Melis et al. 2005; Oades et al. 2005; Piazza and Le Moal 1996; Weiner 2002). DA is also implicated in the regulation of depression, social behavior and pain processing (Kapur and Mann 1992; Wood 2008). DAergic activity changes in a graded fashion over the lifespan, resulting in the manifestation of age-related behavioral profiles and neurological conditions. In rodents, DA-producing neurons begin to form during early mid-gestation (E10.5); at E12.5, these neurons start to express tyrosine hydroxylase, the rate-limiting enzyme in the conversion of L-tyrosine into L-DOPA (3,4-dihydroxyphenylalanine) and, subsequently, into DA. Thereafter, the generation of DAergic cells gradually declines, and importantly, DAergic neurons increasingly undergo two peaks of apoptosis: immediately after birth and again, during the second week of postnatal life (Burke 2004; Oo and Burke 1997). It is estimated that adult human and rat brains contain some 600,000 and 45,000 DAergic cells, respectively (German and Manaye 1993)—a relatively small proportion of the total population of neurons in the brain.

Knowledge of the various transcription factors that contribute to the ontogeny of DAergic neurons has grown considerably in the last decade (Prakash and Wurst 2006). On the other hand, besides knowing that increased levels of reactive oxygen species derived from neurotoxins and that, perhaps, some therapeutic agents can compromise the viability of DA neurons, our understanding of other environmental and physiological factors that are responsible for the survival and demise of these neurons is surprisingly limited. In light of the narrow window within which DAergic cells are born, and the fact that the fate of the developing nervous system is particularly sensitive to environmental influences (Bjorklund and Dunnett 2007), studying how early life events may sculpt DAergic circuits, and therefore predispose individuals, or indeed contribute to their resilience to DA-related disorders later in life, is particularly important.

This article focuses on how early life stress, implicated in a number of behavioral disorders associated with DAergic dysfunction, may exert its effects. Notably, a number of studies, mainly carried out in norepinephrine neurons of adult animals, have shown that glucocorticoids (GC), the primary humoral effectors of the physiological response to stress, can upregulate tyrosine hydroxylase (TH) synthesis and, therefore, as DA production is also under regulation of TH, it is admissible that GCs might also regulate DA production (Makino et al. 2002; Markey et al. 1982; Ortiz et al. 1995, 1996). While these effects are likely to reflect direct GC actions on TH neurons following their activation of GCs receptors (which have transcriptional properties), indirect regulation of TH synthesis through intersecting pathways cannot be excluded (Otten and Thoenen 1975). Administration of GCs significantly change DA and its metabolites levels in the striatum and prefrontal cortex (PFC), importantly, adrenalectomy seems to have an antagonist effect (Lindley et al. 1999; Lindley et al. 2002), although contradictory findings have also been published (Dunn 1988). Nevertheless, it has been shown that dopaminergic transmission in the nucleus accumbens (NAcc) seems to be GC-dependent, both in basal conditions and after stimulus (Barrot et al. 2000).

Programming of behavior by early life stress

Adversity during early life, including physical and emotional neglect and traumatic experiences, can induce persistent effects on physical and mental health (Heim and Nemeroff 2002; Teicher et al. 2003). Specifically, there is now well-documented evidence that adversity in childhood increases the risk for development of conduct disorders, personality disorders, ADHD, major depression, posttraumatic stress disorder, schizophrenia, anxiety, and addictive disorders (Agid et al. 1999; Bernet and Stein 1999; Chapman et al. 2004; Dube et al. 2003; Heim and Nemeroff 2001; Kendler et al. 2004; Weiss et al. 1999; Young et al. 1997). The clinical importance of these findings can be better appreciated when one considers that some 80% of adults who experienced abuse or neglect in early life are predicted to suffer at least one episode of a psychiatric disorder such as depression and anxiety or a behavioral disorder such as addiction (Edwards et al. 2003; Espejo et al. 2007; Gutman and Nemeroff 2003; Heim and Nemeroff 2001; McFarlane et al. 2005). In contrast, the predicted incidence of such disturbances is much lower in women abused as adults (Brown and Moran 1994; McCauley et al. 1997), a finding that points to the existence of critical time windows during which the organism is particularly sensitive to stress-induced pathology later in life.

Most of the above clinical conditions are linked to impaired DAergic transmission and are likely to be underpinned by structural alterations in the nervous tissue which, in turn, translate into a resetting of homeostatic mechanisms that promote either adaptation or pathology. Much attention has been recently focused on the ability of early life stress (ELS) to program the hypothalamic–pituitary–adrenocortical (HPA) axis (Heim et al. 2008; Tarullo and Gunnar 2006). Information about the physical and psychological environments converges on this axis, which, through its secretion of GCs, determines the organism's physiological and behavioral response. In a simplistic way, physical or physiological stress activates the production of corticotrophin-releasing factor in the hypothalamus, which in turns binds to specific receptors in pituitary cells stimulating the production of adrenocorticotropic hormone (ACTH). ACTH is then transported to adrenal glands, culminating with the secretion of GCs (cortisol in humans and corticosterone in rodents). GCs have a series of metabolic effects for improving stress response and act through negative feedback to both the hypothalamus and the anterior pituitary, once the state of stress subsides. Yet, it should be noted that stress response involves far more than the elevation of GCs and, as a consequence, the stress effects cannot be confined to elevations of GCs. Indeed, it has been shown that severe forms of stress can also result in decreased levels of GCs release; as an example, insufficient GC signaling may lie beneath the pathophysiology of some stress-related disorders such as posttraumatic stress disorder (Raison and Miller 2003).

Importantly, in utero exposure to GC/stress has also been found to be associated with long-lasting deficits in cognitive, mood and affective, as well as addictive and affiliative behaviors in humans (French et al. 1999; Heim and Nemeroff 2001; MacArthur et al. 1982; Malaspina et al. 2008; Sinha 2001) and in animal models (Caldji et al.

1998; Liu et al. 1997; Oliveira et al. 2006; Rayburn et al. 1997). It is of interest to note that GC administration or separation of rodents from their mothers during the first week of postnatal life shifts the timing of a number of neurodevelopmental milestones. Such treatments delay the acquisition of neurological reflexes (e.g. righting and postural reflexes, negative geotaxis) that depend on vestibular and cerebellar function (Ellenbroek et al. 2005; Mesquita et al. 2007), while advancing eye and ear opening. On the other hand, prenatal stress advances the time of ear-flap and eye opening (Secoli and Teixeira 1998). While these neurodevelopmental changes may reflect delayed myelination (Ferguson and Holson 1999; Murphy et al. 2001; Valkama et al. 2000), there is strong evidence for a role of altered catecholaminergic transmission in the vestibular region, the ventral tegmental area (VTA) and raphe nuclei (Mesquita et al. 2007). Since these brainstem structures project to corticolimbic structures, it is plausible that their altered activity impacts on neuroendocrine (HPA axis activity) and behavioral functions.

In the majority of cases, the behavioral consequences of ELS are attributable to transient or persistent dysregulation of GC secretion which, in turn, is causally related to increased susceptibility to depression and anxiety disorders (Carroll et al. 1976; Heim et al. 2001; Heim et al. 2000; Holsboer 2001; Yehuda et al. 1991), impaired social behaviors (Rinne et al. 2002), ADHD (Sullivan and Brake 2003; Swanson et al. 2007), and drug abuse (Huizink et al. 2006; Prendergast and Little 2007), all of which appear to involve an altered DAergic tone. Yet, whereas severe stress is usually associated with HPA-mediated pathology, mild stressful experiences may be linked to "positive" effects and/or resilience in rodents (Catalani et al. 1993; Levine 1957; Macri et al. 2009).

Pioneering work by Meaney and colleagues showed that the HPA axis can be epigenetically programmed (McGowan et al. 2009; Weaver et al. 2004) and further, that epigenetic (methylation) marks may be transmitted across generations. Other studies have shown that ELS-induced alterations in the epigenetic control of the activity of the HPA axis are associated with enduring expression of impaired cognitive- and depressive-like behavior in rodents (Murgatroyd et al. 2009). It remains to be demonstrated whether drugs with the potential to reverse DNA methylation (e.g. 5-aza-2′-deoxycytidine, already approved for use in cancer chemotherapy), can reverse the central effects of ELS. It should be noted that stress also leads to transient epigenetic alterations by deacetylation of histones with concomitant changes in behavior; such changes are drug-reversible with inhibitors of histone decaetyltransferase which have also proved effective in reversing age-dependent cognitive decline in experimental animals (Peleg et al. 2010).

Linking ELS to DAergic activity

The developing postnatal and adolescent brain is characterized by high levels of neuroplasticity and reorganization. Given the evidence that prenatal, perinatal, and early postnatal life represent windows of susceptibility to the long-lasting effects of stress on brain pathologies related to DAergic dysfunction, it is reasonable to assume that DAergic circuits are direct or indirect targets of stress and stress hormones (GC). The clinical studies about ELS, DAergic transmission and psychiatric conditions are sparse. Nevertheless, it has been shown that low parental care is associated with higher cortisol and, consequently, ventral striatum dopamine levels in response to a psychosocial stress task (Pruessner et al. 2004). Moreover, it has been shown that a polymorphism in the DA enzyme COMT and childhood trauma may interact together to contribute to the risk of developing psychopathological personality traits (Savitz et al. 2010). COMT polymorphisms also seem relevant for the manifestation of depressive symptoms in children exposed to severe social deprivation (Drury et al. 2010) and for the modulation of emotionality in sexually abused children (Perroud et al. 2010). A functional polymorphism that leads to higher expression of the enzyme monoamine oxidase A (degrades DA), was found to be correlated with reduced propensity for anti-social behaviors in maltreated children (Caspi et al. 2002; Kim-Cohen et al. 2006). Altogether, these findings reveal that variations in DA metabolism may modulate the impact of early life adversity on behavior and suggest a close link between DA, stress and mental illness. Stress may influence DAergic (1) cell fate; (2) neuron metabolism (DA production and turnover); (3) neuron morphology; and/or (4) receptor expression and synaptic transmission. Its effects, whether transient or permanent, can thus be expected to have long-term consequences on the shaping and expression of DA-regulated behaviors. Notably, the consequences of ELS appear to be different upon the different DAergic circuits. Perinatal stress seems to decrease steady state levels of DA in the PFC and to increase it in both the NAcc and striatum (Boksa and El-Khodor 2003). While perinatal anoxia enhances stress-induced DA release in the NAcc, it seems to blunt it in the PFC (Brake et al. 1997; 2000), which strongly suggests different vulnerabilities of the mesocortical, mesolimbic, and nigrostriatal pathways to the deleterious effects of stress. A different timing of development and maturation of neurons of each circuit or different intrinsic sensibilities may explain these differences, although this needs to be further explored.

DAergic neurons show marked anatomical and functional heterogeneity. They are principally located in the diencephalon, mesencephalon, and olfactory bulb (Bjorklund and Dunnett 2007); the largest number (~90%) is found in the

ventral part of the mesencephalon. These mesencephalic neurons are the origin of the so-called mesocortical, mesolimbic, and nigrostriatal DAergic systems (Fig. 1); a fourth set of DAergic neurons, less relevant to this article, follow the tuberoinfundibular pathway to terminate in the hypothalamo–pituitary unit. Both the mesolimbic and mesocortical systems arise from the VTA. While the mesocortical pathway terminates in the cortex, where it is thought to control cognition and executive functioning, the mesolimbic projections innervate limbic areas such as the nucleus accumbens (NAcc), amygdala and hippocampus and serve in the regulation of memory, motivation, reward and addiction. Due to their common origins in the VTA, these two pathways are jointly referred to as the mesocorticolimbic system, although the activity of each is subject to regulation by distinct feedback loops. DAergic neurons that project from the substantia nigra to the striatum comprise the nigrostrial system; this pathway is mainly implicated in the initiation and maintenance of motor behavior. As already mentioned, these midbrain DAergic neurons are formed during early development, according to a rostrolateral to caudomedial gradient (Bayer et al. 1995) and their fibers project to terminal fields in the mesocortical and nigrostrial areas (Kawano et al. 1995). All these DAergic systems are thought to be fully mature and functional by the first few weeks of postnatal life in both rats (Voorn et al. 1988) and humans (Prakash and Wurst 2006), although some others have suggested that this maturation can occur until early adulthood in the PFC for example (Benes et al. 2000).

Indicating that the developing and maturing DAergic systems are highly sensitive to perturbations, including stress and high levels of GC, experiments from our laboratory found that GC administration during late gestation (E18–19) significantly increases the ratio of apoptotic to proliferative cells in the VTA, resulting in a

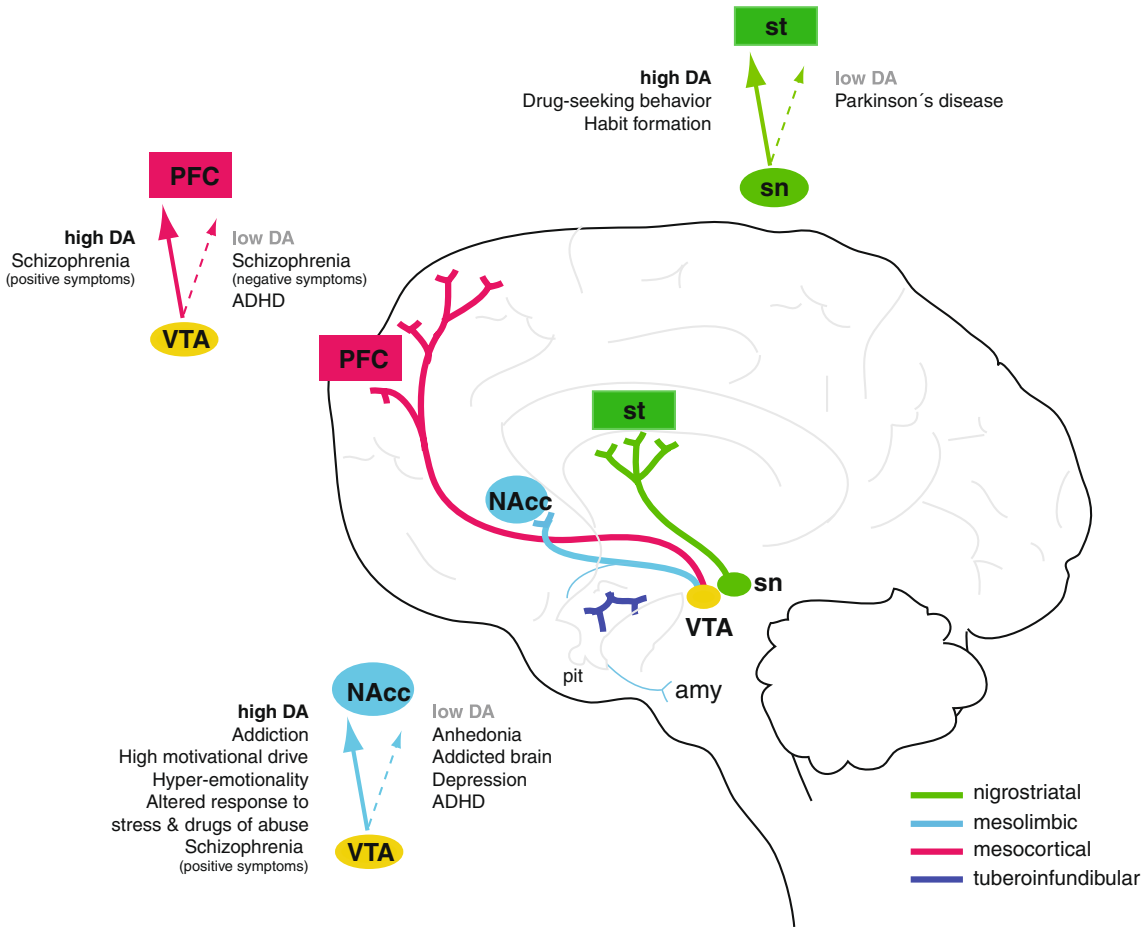

Fig. 1 DAergic pathways of the brain. The mesolimbic and mesocortical pathways arise from the VTA, which lies close to the substantia nigra (*sn*). The mesolimbic pathway projects especially to the nucleus accumbens (*NAcc*), but also to the amygdala (*amy*). The mesocortical pathway projects to the prefrontal cortex (*PFC*). The tuberoinfundibular tract terminates in the hypothalamo–pituitary (*pit*) unit. The nigrostriatal pathway projects from sn to striatum (*st*). Altered dopaminergic tone in each of these circuits (either hypo- or hyperactivity) is associated with a particular pathological condition. *ADHD* attention deficit hyperactivity disorder

sustained decrease in DAergic inputs to the NAcc (Leao et al. 2007). The same treatment altered a number of DA-regulated behaviors, including anxiety (Oliveira et al. 2006), prepulse inhibition and drug preference (Leão, Rodrigues et al., unpublished observations). Some of these behavioral changes might be additionally explained by prenatal stress-induced variations in DA turnover in the PFC (Fride and Weinstock 1988) and NAcc (Alonso et al. 1994), reflected in altered sensitivity to certain drugs of abuse. Remarkably, ELS also adjusts DAergic tone in response to certain drugs of abuse and to stress. For example, progeny from stressed dams display higher NAcc DA output under basal conditions and in response to amphetamine or cocaine exposure (Kippin et al. 2008; Silvagni et al. 2008). Similarly, maternal separation (MS) enhances DA release in the NAcc following amphetamine administration (Hall et al. 1999; Moffett et al. 2006). Variations in MS and handling cause changes in ethanol and cocaine self-administration with concomitant changes in DA receptors in the NAcc (Moffett et al. 2007). A short-term insult such as perinatal anoxia results in long-term alterations in the NAcc DAergic response to tail-pinch (Brake et al. 1997). ELS also affects DA transporter (DAT) and DA receptor expression, function and sensitivity. The role of DAT1 which regulates DAergic tone by clearing DA in the synaptic cleft may be significant in this respect; this is exemplified by the fact that drugs such as cocaine induce pleasurable feelings by inhibiting DAT1 activity. In this vein, it is interesting to note that MS decreases DAT levels in the NAcc (Brake et al. 2004; Meaney et al. 2002).

Besides their well-described ability to determine neuronal cell fate (Yu et al. 2010) and neuronal morphology in the hippocampus (Fujioka et al. 2006; Seidel et al. 2008; Sousa et al. 2000) and PFC (Bock et al. 2005; Cerqueira et al. 2007a; Cerqueira et al. 2007b; Michelsen et al. 2007; Murmu et al. 2006), stress (early or in adulthood) and GCs have been found to influence the morphology of neurons in the mesocorticolimbic circuitry. In the above-mentioned study by Leao et al. (2007), we observed that GC during late gestation results in a significant reduction in the volume of the NAcc with significant changes in spine density and morphology (Leão, Rodrigues et al., unpublished observations). These findings were extended by recent work from Martinez-Tellez et al. (2009) who demonstrated decreased spine densities in the NAcc and hippocampus of the progeny of rat dams subjected to restraint stress from mid-late gestation. Since spine density and morphology correlates with synaptic transmission and plasticity (Blanpied and Ehlers 2004; Luscher et al. 2000; Murthy et al. 2001), these findings indicate that ELS interferes with transmission at neuronal networks. Interestingly, however, prenatal stress has been shown to alter the relative number of mushroom spines in the PFC (Michelsen et al. 2007); as compared to other spine types, mushroom spines are relatively stable, i.e., do not show spontaneous appearance and disappearance, suggesting a mechanism through which early life manipulations of the GC milieu might leave a permanent trace within mesocorticolimbic pathways.

As mentioned earlier, there is a convincing correlation between adverse experience during early life and depression (Edwards et al. 2003; Felitti et al. 1998; McCauley et al. 1997). Given that the therapeutic efficacy of the antidepressant tricyclic drugs was based on their ability to inhibit norepinephrine (NE) and serotonin (5-HT) transporters, the role of dopamine in depression was less explored over the years. Yet, ELS has long-term effects not only on noradrenergic and serotonergic but also on DAergic circuits (Schneider et al. 1998; Takahashi et al. 1992). Research, based on measurements of DA metabolites, suggests that a hypo-DAergic state may be causally related to the depressed state; for example, depressed patients display reduced cerebrospinal fluid levels of homovanillic acid (Mendels et al. 1972) and levels of dihydroxyphenylacetic acid (DOPAC) are reduced in the caudate, putamen, and NAcc of depressed suicide victims (Bowden et al. 1997). Hypofunction of the mesocorticolimbic DA system is thought to underlie anhedonia, a cardinal symptom in depression, as well as the loss of motivation experienced by subjects suffering from cognitive and mood disturbances. Interestingly, boosting DA levels through administration of L-DOPA to Parkinsonian patients improves their depressive symptoms (Maricle et al. 1995), and antidepressant drugs that increase DAergic transmission (inhibitors of monoamine oxidase inhibitors, catechol-*O*-methyltransferase, DA reuptake, and DA receptor agonists) have mood-improving effects (Papakostas 2006). It should be noted, however, that other authors failed to observe any antidepressant actions of L-DOPA (Cools 2006; Shaw et al. 1980). Again, it is important to highlight that disruption of other monoamines transmission such as NE may underlie depression basic symptoms. In fact, drugs that act selectively to enhance either DA or NE transmission can produce a clear antidepressant action; moreover, DA is able to modulate noradrenergic transmission and vice-versa (El Mansari et al. 2010). Importantly, some strategies acting on both systems have been shown to be more effective, not only in drug naive patients, but also in treatment-resistant depression (El Mansari et al. 2010).

Schizophrenia, a neurodevelopmental disorder in which symptoms are first seen in teenagers and young adults, is clearly associated with disturbed DAergic tone. Childhood malnutrition and viral infection, as well as obstetric complications or genetic defects are thought to be triggers of the disease (Bayer et al. 1999; Cannon et al. 2003; Murray and Fearon 1999), although in the more recent "two-hit" hypothesis on the origins of schizophrenia, stress during

young adulthood has been added to the list of aforementioned neurodevelopmental factors in disease causation (Bayer et al. 1999; Malaspina et al. 2008; Pantelis et al. 2003). Indeed, the role of stress in schizophrenia has recently received support from studies in humans (Weber et al. 2008) and animals (Choi et al. 2009). Currently, the leading hypothesis is that a deficit in DA activity at D1 receptors in the PFC is responsible for the cognitive impairment and negative symptoms of schizophrenia, while hyperstimulation of D2 receptors by subcortical (mesolimbic) DA is responsible for core ("positive") disease symptoms (hallucinations, delusions) (Toda and Abi-Dargham 2007).

Early life adversity such as lead exposure, drug abuse (smoking, alcohol, cannabis), low birth weight or premature birth can increase the risk for developing ADHD, although genetic factors also play a substantial role on its etiology (Sullivan and Brake 2003; Swanson et al. 2007). A dysfunction of DAergic mesocortical (but also mesolimbic (Russell et al. 1995)) transmission is thought to underlie ADHD, though the involvement of other neurotransmitters such as noradrenaline has to be considered (Oades et al. 2005). Briefly, hypofunctioning (especially) of the DAergic transmission in the right PFC seems to occur in ADHD, and this is particularly interesting since ELS can induce lateralized changes on PFC DAergic function (Fride and Weinstock 1988). Other findings support the involvement of DA in ADHD: (1) changes in DAT expression were found in ADHD patients compared to controls (Dougherty et al. 1999); (2) genetic analysis identified an association between specific alleles of D4 receptor (Faraone et al. 2001; Rowe et al. 1998) and of DAT (Waldman et al. 1998) with ADHD, and (3) the use of methylphenidate which blocks DA reuptake into the cell by the DAT as the most common treatment for ADHD.

Besides its role in specific types of behavior, the DAergic mesocortical pathway seems to be particularly important in buffering HPA-response to stress. This circuit frequently shows functional hemispheric asymmetry that can be modulated by early life adversity. For example, DA metabolism is significantly higher in the right infralimbic cortex of handled pups (positive stress) than non-handled, and this has been suggested to underlie, in part, to their superior capacity to adapt to stress and restraint HPA activity (Sullivan and Dufresne 2006).

It emerges from the above brief overview that ELS may result in either hyper- or hypoactivity of DAergic systems. Thus, increased DA transmission in the mesolimbic system may result in schizophrenia and increased fear, respectively, whereas reduced DA activity in mesocorticolimbic circuits may lead to memory (hippocampus and frontal cortex) and mood (frontal cortex/ventral striatum) deficits (Fig. 1). Notably, hypoactivity in the hippocampus will likely result in increased GC secretion which, in turn will exacerbate neuronal dysfunction and behavioral anomalies. On the other hand, stress-induced hypoactivity in the mesocorticolimbic DAergic system is likely to enhance novelty-seeking and addictive behaviors, a subject that will be dealt with in greater detail in the following section.

ELS targets mesocorticolimbic DAergic circuits: impact on additive behavior

Despite their diverse chemical structures, cellular mechanisms of action and physiological and behavioral manifestations, all drugs of abuse share a common property: they all act as positive reinforcers and, as a consequence, induce addiction. Increased DA release in the NAcc characterizes drug reinforcement, but also other consumatory behaviors such as sex and food; thus the VTA-NAcc pathway is appropriately also known as the "reward pathway" (Piazza and Le Moal 1996). Subjective feelings of "pleasure" or hedonia after consummation are experienced as a result of parallel activation of mesocortical DAergic circuits. Though traditionally DA is seen as responsible for the "liking" part of a reward, more recently it has been suggested that DA is not essential/sufficient to mediate changes in hedonic behavior. In fact, DA seems to contribute substantially for incentive salience, i.e., the "wanting" part of the process rather than the "liking" part (Berridge 2007). Nevertheless, one way or another, DAergic transmission is certainly playing a vital role in the rewarding process. Perusal of the literature indicates that an apparently intricately-regulated balance between hypo- and hyper-DAergic states underlies an individual's cycles of drug-seeking behavior and abuse. Thus, hyper-DAergic states seem to enhance the motivational or rewarding properties of drugs of abuse and hypo-DAergic states appear to enhance drug-seeking behavior in parallel with reductions in the perceived motivational impact of "natural" rewards such as food and sex (Diana et al. 1998; Diana et al. 1993; Melis et al. 2005; Parsons et al. 1991).

In the context of this review, it is interesting to note that stress or GC in adulthood enhance DA release in the NAcc (Kalivas and Duffy 1995; Rouge-Pont et al. 1998; Takahashi et al. 1998; Thierry et al. 1976) and increase the strength of excitatory synapses on mesencephalic DA neurons (Saal et al. 2003), while inducing similar patterns of dendritic organization in the NAcc (Liston et al. 2006; Robinson et al. 2001; Robinson and Kolb 1999). Drugs of abuse and stress display other common biobehavioral features: while repeated exposure to the same (Kalivas and Stewart 1991) or novel stressors (Dallman et al. 1994) leads to "facilitation" or "sensitization" of behavioral responses, stress as well as drugs of abuse (Robinson and Becker 1986; Sorg and Kalivas 1991; Stewart and Badiani

1993) are accompanied by augmented DA release in the NAcc (Doherty and Gratton 1992; Kalivas and Stewart 1991). Several other lines of evidence derived from animal studies suggest that stress and GC may act, like drugs of abuse, to induce positive reinforcement: (1) GC facilitate the psychomotor stimulant effects of cocaine, amphetamine and morphine (Cools 1991; Marinelli et al. 1994); (2) depletion of GC by adrenalectomy reduces drug and alcohol consumption (Fahlke et al. 1994; Marinelli and Piazza 2002; Marinelli et al. 1997a; 1997b); (3) GC levels before drug self-administration are positively correlated with the extent of low-dose self-administration of cocaine (Goeders and Guerin 1994; Piazza et al. 1991); and (4) naive rats self-administer GC in a dose-related manner (Piazza et al. 1993).

Addiction is determined by a number of factors other than the intrinsic properties of a given drug. In an interesting series of studies aimed at understanding individual differences in predisposition to drug abuse, Piazza and colleagues found that the liability of rats to self-administer drugs can be predicted by the response of mesolimbic DAergic neurons to stress; specifically, animals that were more sensitive to the DA-releasing actions of stress were more likely to display addictive behavior (Piazza and Le Moal 1996; Piazza et al. 1991). Polymorphisms in the human DA receptor 2 (Blum et al. 1990; Noble 2000) and DA receptor 1 (Batel et al. 2008; Huang et al. 2008) have been associated with increased propensity to alcohol and other substances of abuse, gambling, and compulsive shopping; however, there is no information available with respect to the physiological responses of the affected individuals to stressful stimuli. Val158Met polymorphism in catechol-*O*-methyltransferase gene, which is involved in DA degradation, has been associated with schizophrenia, bipolar disorder, and also with substance abuse, although some other studies have failed to prove so (Hosak 2007). Exposure to both, drugs with abuse potential and stress trigger neuroadaptative changes in DAergic circuits that ultimately determine neurochemical and behavioral responses. This indicates that the activities of addiction-related DAergic pathways are subject to programming by lifetime experiences, with the final neurochemical and behavioral phenotype reflecting both genetics and experiential history.

Early life adversity, i.e., during the ontogeny of mesocorticolimbic DAergic systems, has been repeatedly shown to induce addiction to a variety of drugs of abuse in adult animals; a few examples from the literature follow: (1) exposure of dams to restraint stress leads to persistent behavioral and neurobiological alterations that are associated with increased consumption of psychostimulants in the adult offspring (Kippin et al. 2008); (2) animals stressed during prenatal life display earlier sensitization to the behavioral effects of amphetamine, although their motor responses to the drug do not differ from those of non-stressed animals (Henry et al. 1995); (3) separation of pups from their mothers and/or littermates during the early postnatal period, a procedure that leads to hypersecretion of GC (Ladd et al. 2000; Liu et al. 1997; Mesquita et al. 2007), advances the time of acquisition of cocaine self-administration (Moffett et al. 2006) and enhances cocaine-induced locomotor activity as well as behavioral sensitization (Brake et al. 2004; Kikusui et al. 2005; Li et al. 2003); and (4) MS stress also increases alcohol and drug consumption during adulthood although handling or brief MS—a manipulation that results in reduced GC secretion and responses to stress (de Kloet et al. 1996; Levine 1967)—decreases voluntary ethanol intake (Huot et al. 2001; Ploj et al. 2003). Though human studies are sparse, it has been shown that childhood adversity is associated with blunted subjective responses to reward-predicting cues as well as dysfunction in left basal ganglia regions implicated in reward-related learning and motivation (Dillon et al. 2009), suggesting that in humans ELS can also change the impact of a reward.

The above examples illustrate the impact that ELS can have on the development of addictive behavior and reinforce the view that the neuronal circuits involved in the regulation of such behavior are particularly vulnerable to programming by stress and GC during the prenatal, perinatal, and early postnatal periods. Part of these effects are, as already mentioned, mediated by stress and GC participating in the regulation of the birth and maturation and DAergic cells in the mesolimbic system (Kawamura et al. 2006; Leao et al. 2007). We also noted that the adult progeny of dams stressed during gestation have significantly fewer TH-positive (DAergic) fibers of the NAcc (Leao et al. 2007). Interestingly, these presumably hypo-DAergic animals were recently found to have a greater propensity for developing drug-seeking behaviors (Leão, Rodrigues et al., unpublished observations). The above findings may be explained, at least partly, in terms of hypersensitivity to the DA-releasing effects of drugs of abuse, evidenced by the increased release of DA in response to amphetamine or cocaine in rats that have either experienced prenatal stress (Kippin et al. 2008; Silvagni et al. 2008) or maternal deprivation stress in the first postnatal days (Hall et al. 1999).

Finally, alterations in the thresholds required for activation of DA type-1 (D1) and type-2 (D2) receptors by DA (Volkow et al. 2004) could represent a potential mechanism through which ELS causes drug-seeking behavior and ultimately, addiction. One hypothetical model predicts that the ratio of D1 to D2 receptors in the NAcc determines the sensitivity to "natural rewards" vs. the proclivity to "seek for pleasure" through drug abuse (Volkow et al. 2004). Earlier studies in rats described late gestational stress-

induced increases in the expression and ligand-binding capacity of D2 receptors in the frontal cortex, hippocampus, and core of the NAcc (Berger et al. 2002), with concomitant decreases in the number of D1 receptors in the NAcc. More recently, we observed that the offspring of mothers exposed to exogenous GC in the last trimester of gestation, display diminished DA levels in the NAcc and other mesolimbic structures, an altered D1/D2 ratio and, interestingly, proneness to addictive behaviors (Leão, Rodrigues et al., unpublished observations).

Together, the results summarized above demonstrate that ELS has sustained effects on the morphology and activity of mesolimbic and mesocortical DAergic circuits, accompanied by altered sensitivity and vulnerability to drugs of abuse. In the next section, we will consider the role of the nigrostriatal DAergic pathway which has received relatively little attention in the context of drug abuse. Considering the long-lasting changes in DA receptors expression in several models of early life stress, we may raise the hypothesis that these genes may be transcriptional targets of GCs/stress or that they may undergo epigenetic regulation in response to early life adversity.

A new player in addiction: the nigrostriatal DAergic pathway?

As recently reviewed by Wise (2009), the nigrostriatal DAergic system, best known for its role in motor control and Parkinson's disease pathology, also seems to play an important role in addictive disorders. First hints were provided by the observations that electrical stimulation of nigrostriatal DAergic cells and terminal fields produced rewarding effects (Crow 1972; Prado-Alcala and Wise 1984; Wise 1981) and that selective lesions of the nigrostriatal pathway attenuated drug self-administration (Glick et al. 1975; Linseman 1976). Those early studies have been backed up by the results of further experimentation (Suto et al. 2004), including the demonstration that intra-nigral infusions of D1 receptor antagonists reduce drug self-administration (Quinlan et al. 2004).

Current views suggest that the contributions of the mesolimbic and nigrostriatal DAergic systems to the development of addiction are distinctly separated in time. Thus, whereas the mesolimbic pathway (especially the NAcc core) is responsible for the rewarding effects of drugs during the initial phases of addiction, the nigrostriatal system assumes an increasingly important role at later stages as drug consumption increases (Everitt et al. 2008; Everitt and Robbins 2005; Wise 2009). The NAcc core is important not only for the rewarding effect of drugs of abuse (Wise 2004) but also mediates the motivational drive or "wanting of a reward" that underlies drug-craving (Berridge 2007), and assures efficiency of response-outcome associative learning (Pavlovian conditioning; Yin and Knowlton 2006). However, second-order protocols of drug reinforcement and pharmacological experiments revealed that the dorsal striatum, rather than the NAcc, is essential for drug-seeking behavior after repetitive drug exposure (Ito et al. 2000). This interpretation is consistent with earlier work which showed that, while dorso-striatal lesions do not affect acquisition of Pavlovian responses (Taylor and Robbins 1986), infusion of DAergic antagonists into the dorsal striatum decreases drug-seeking under second-order drug reinforcement protocols (Vanderschuren et al. 2005). These findings have led to the concept that repetitive exposure to drugs of abuse evolve from being goal-directed behaviors into habit-based actions (Everitt et al. 2008; Everitt and Robbins 2005; Wise 2009). Self-administration protocols in monkeys have confirmed the progressive shift from goal-directed (Pavlovian) behaviors (facilitated by the NAcc in cooperation with associative cortico-basal ganglia networks) to habit-based (instrumental) actions that depend on the dorsal striatum (in particular, the dorso-lateral striatum, an integral component of the sensorimotor cortico-basal ganglia pathway (Porrino et al. 2004)).

The new knowledge concerning the contribution of the nigrostriatal DAergic pathway in drug addiction has been now extended to provide further new insights into how stress increases vulnerability to drug abuse behavior. Functional imaging studies in cocaine addicts have revealed a positive correlation between activation of the dorsal striatum by stress and the degree of cocaine craving (Sinha et al. 2005), and our own studies have demonstrated that stress promotes habit-based decisions in rats by increasing activation of the sensorimotor cortico-basal ganglia pathway (Dias-Ferreira et al. 2009); the latter results are reminiscent of the effects of repetitive drug administration.

Albeit several studies have shown that ELS can affect the mesolimbic circuit, the consequences in the nigrostriatal circuit remain poorly studied and understood. Prenatal DEX exposure increases TH+cell numbers in the substantia nigra, demonstrating that this region can be profoundly affected in terms of DAergic transmission (McArthur et al. 2005). Furthermore, it was shown that ELS can make dopamine neurons from the nigrostriatal pathway to become more susceptible to subsequent insults later in life (Pienaar et al. 2008). Nonetheless, due to the paucity of studies, the direct effect(s) of ELS in the development/maturation of this circuit and its relevance for addiction for example, remains to be determined.

Future perspectives

The available literature, in a rather fragmented way, suggests an association between ELS, DA transmission, and mental

illness. Yet, it remains to be answer if the DAergic dysfunction is causal, or merely a consequence, of ELS and in several of the psychiatric conditions linked to ELS. Part of the problem relies on "snapshot approach" that is commonly used in the available studies that precludes the understanding of the dynamics of the insult-response-adaptation process. Thus, we believe that one of the priorities in the field should be to perform longitudinal studies that establish a direct link between altered DAergic transmission and specific endophenotypes for each of the pathological conditions in which ELS is implicated. In parallel, a longitudinal multimodal characterization of ELS exposure in the mesolimbic, mesocortical, or nigrostriatal DAergic pathways is needed. If this is achieved, ultimately, we could determine what the windows of vulnerability of each of these DAergic pathways are and which is more affected in each type of ELS. Furthermore, it could help us understand the long-term impact, and the adaptations, of the distinct DA pathways in neuropsychiatric conditions in which ELS is implicated. As an example, for addiction studies, this integrated approach would allow for a better insight on the role of different DA pathways throughout the different phases of addictive behavior. Moreover, this would give insights on how neurons in each of these pathways respond to drugs of abuse and/or stress in both animal models of ELS and human subjects and how these can be therapeutically modulated. Importantly, this approach is useful and applicable to many neuropsychiatric conditions.

Conclusions

Evidence for the persistent morphological, neurochemical and behavioral impact of elevated GC levels (pharmacologically or stress-induced) during development illustrates the importance of gene X environment (epigenetic) interactions in the etiology of psychiatric conditions. In light of the ontogenetic development of the mesocorticolimbic and nigrostriatal DAergic systems, reports that prenatal stress or manipulations of the maternal GC *milieu* and postnatal stress (ELS) may be causal to behavioral disorders ascribed to dysfunctional DAergic transmission (e.g., schizophrenia, drug addiction and possibly, depression) are not surprising. Having identified some of the neurobiological substrates that underpin the behavioral anomalies, the immediate challenge is to decipher the molecular and cellular mechanisms that underwrite these changes. Such studies will provide the conceptual basis for devising pharmacological interventions to ameliorate the undesired behavioral outcomes of mal-programmed DAergic circuits. Meanwhile, the existing literature suggests that serious psychiatric conditions in later life are preventable through the judicious use of GC in obstetrics and neonatal medicine, by avoiding stress during pregnancy and by placing emphasis on early parental care.

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