

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	42
GC	Glucocorticoids	43
VTA	Ventral tegmental area	46
NAcc	Nucleus accumbens	48

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.

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

95 This article focuses on how early life stress, implicated
96 in a number of behavioral disorders associated with
97 DAergic dysfunction, may exert its effects. Notably, a
98 number of studies, mainly carried out in norepinephrine
99 neurons of adult animals, have shown that glucocorticoids
100 (GC), the primary humoral effectors of the physiological
101 response to stress, can upregulate tyrosine hydroxylase
102 (TH) synthesis and therefore as DA production is also
103 under regulation of TH, it is admissible that GCs might also
104 regulate DA production (Makino et al. 2002; Markey et al.
105 1982; Ortiz et al. 1996). While these effects are likely to
106 reflect direct GC actions on TH neurons following their
107 activation of glucocorticoid receptors (which have tran-
108 scriptional properties), indirect regulation of TH synthesis
109 through intersecting pathways cannot be excluded (Otten
110 and Thoenen 1975). Administration of GCs significantly
111 change DA and its metabolites levels in the striatum and
112 prefrontal cortex (PFC), importantly, adrenalectomy seems
113 to have an antagonist effect (Lindley et al. 1999; Lindley et
114 al. 2002), although contradictory findings have also been
115 published (Dunn 1988). Nevertheless, it has been shown
116 that dopaminergic transmission in the nucleus accumbens
117 (NAcc) seems to be GC-dependent, both in basal conditions
118 and after stimulus (Barrot et al. 2000).

119 **Programming of behavior by early life stress**

120 Adversity during early life, including physical and emotional
121 neglect and traumatic experiences, can induce persistent
122 effects on physical and mental health (Heim and Nemeroff
123 2002; Teicher et al. 2003). Specifically, there is now well-
124 documented evidence that adversity in childhood increases
125 the risk for development of conduct disorders, personality
126 disorders, ADHD, major depression, posttraumatic stress
127 disorder, schizophrenia, anxiety, and addictive disorders

(Agid et al. 1999; Bernet and Stein 1999; Chapman et al. 128
2004; Dube et al. 2003; Heim and Nemeroff 2001; Kendler 129
et al. 2004; Weiss et al. 1999; Young et al. 1997). The 130
clinical importance of these findings can be better appreci- 131
ated when one considers that some 80% of adults who 132
experienced abuse or neglect in early life are predicted to 133
suffer at least one episode of a psychiatric disorder such as 134
depression and anxiety or a behavioral disorder such as 135
addiction (Edwards et al. 2003; Espejo et al. 2007; Gutman 136
and Nemeroff 2003; Heim and Nemeroff 2001; McFarlane et 137
al. 2005). In contrast, the predicted incidence of such 138
disturbances is much lower in women abused as adults 139
(Brown and Moran 1994; McCauley et al. 1997), a finding 140
that points to the existence of critical time windows during 141
which the organism is particularly sensitive to stress-induced 142
pathology later in life. 143

144 Most of the above clinical conditions are linked to
145 impaired DAergic transmission and are likely to be
146 underpinned by structural alterations in the nervous tissue
147 which, in turn, translate into a resetting of homeostatic
148 mechanisms that promote either adaptation or pathology. 149
Much attention has been recently focused on the ability of
150 early life stress (ELS) to program the hypothalamic–
151 pituitary–adrenocortical (HPA) axis (Heim et al. 2008;
152 Tarullo and Gunnar 2006). Information about the physical
153 and psychological environments converges on this axis,
154 which, through its secretion of glucocorticoids (GCs),
155 determines the organism's physiological and behavioral
156 response. In a simplistic way, physical or physiological
157 stress activates the production of corticotrophin-releasing
158 factor in the hypothalamus, which in turns binds to
159 specific receptors in pituitary cells stimulating the produc-
160 tion of adrenocorticotrophic hormone (ACTH). ACTH is
161 then transported to adrenal glands, culminating with the
162 secretion of GCs (cortisol in humans and corticosterone in
163 rodents). GCs have a series of metabolic effects for
164 improving stress response and act through negative
165 feedback to both the hypothalamus and the anterior
166 pituitary, once the state of stress subsides. Yet, it should
167 be noted that stress response involves far more than the
168 elevation of GCs and, as a consequence, the stress effects
169 cannot be confined to elevations of GCs. Indeed, it has
170 been shown that severe forms of stress can also result in
171 decreased levels of GCs release; as an example, insuffi-
172 cient GC signaling may lie beneath the pathophysiology of
173 some stress-related disorders such as posttraumatic stress
174 disorder (Raison and Miller 2003).

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

181 1998; Liu et al. 1997; Oliveira et al. 2006; Rayburn et al.
 182 1997). It is of interest to note that GC administration or
 183 separation of rodents from their mothers during the first
 184 week of postnatal life shifts the timing of a number of
 185 neurodevelopmental milestones. Such treatments delay the
 186 acquisition of neurological reflexes (e.g. righting and
 187 postural reflexes, negative geotaxis) that depend on
 188 vestibular and cerebellar function (Ellenbroek et al.
 189 2005; Mesquita et al. 2007), while advancing eye and
 190 ear opening. On the other hand, prenatal stress advances
 191 the time of ear-flap and eye opening (Secoli and Teixeira
 192 1998). While these neurodevelopmental changes may
 193 reflect delayed myelination (Ferguson and Holson 1999;
 194 Murphy et al. 2001; Valkama et al. 2000), there is strong
 195 evidence for a role of altered catecholaminergic transmis-
 196 sion in the vestibular region, the ventral tegmental area
 197 (VTA) and raphe nuclei (Mesquita et al. 2007). Since these
 198 brainstem structures project to corticolimbic structures, it
 199 is plausible that their altered activity impacts on neuroen-
 200 docrine (HPA axis activity) and behavioral functions.

201 In the majority of cases, the behavioral consequences of
 202 ELS are attributable to transient or persistent dysregulation
 203 of GC secretion which, in turn, is causally related to
 204 increased susceptibility to depression and anxiety disorders
 205 (Carroll et al. 1976; Heim et al. 2001; Heim et al. 2000;
 206 Holsboer 2001; Yehuda et al. 1991), impaired social
 207 behaviors (Rinne et al. 2002), ADHD (Sullivan and Brake
 208 2003; Swanson et al. 2007), and drug abuse (Huizink et al.
 209 2006; Prendergast and Little 2007), all of which appear to
 210 involve an altered DAergic tone. Yet, whereas severe stress
 211 is usually associated with HPA-mediated pathology, mild
 212 stressful experiences may be linked to “positive” effects
 213 and/or resilience in rodents (Catalani et al. 1993; Levine
 214 1957; Macri et al. 2009).

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

Linking ELS to DAergic activity

234

235 The developing postnatal and adolescent brain is charac-
 236 terized by high levels of neuroplasticity and reorganization.
 237 Given the evidence that prenatal, perinatal, and early
 238 postnatal life represent windows of susceptibility to the
 239 long-lasting effects of stress on brain pathologies related to
 240 DAergic dysfunction, it is reasonable to assume that
 241 DAergic circuits are direct or indirect targets of stress and
 242 stress hormones (GC). The clinical studies about ELS,
 243 DAergic transmission and psychiatric conditions are sparse.
 244 Nevertheless, it has been shown that low parental care is
 245 associated with higher cortisol and, consequently, ventral
 246 striatum dopamine levels in response to a psychosocial
 247 stress task (Pruessner et al. 2004). Moreover, it has been
 248 shown that a polymorphism in the DA enzyme COMT and
 249 childhood trauma may interact together to contribute to the
 250 risk of developing psychopathological personality traits
 251 (Savitz et al. 2010). COMT polymorphisms also seem
 252 relevant for the manifestation of depressive symptoms in
 253 children exposed to severe social deprivation (Drury et al.
 254 2010) and for the modulation of emotionality in sexually
 255 abused children (Perroud et al. 2010). A functional
 256 polymorphism that leads to higher expression of the
 257 enzyme monoamine oxidase A (degrades DA), was found
 258 to be correlated with reduced propensity for anti-social
 259 behaviors in maltreated children (Caspi et al. 2002; Kim-
 260 Cohen et al. 2006). Altogether, these findings reveal that
 261 variations in DA metabolism may modulate the impact of
 262 early life adversity on behavior and suggest a close link
 263 between DA, stress and mental illness. Stress may influence
 264 DAergic (1) cell fate; (2) neuron metabolism (DA produc-
 265 tion and turnover); (3) neuron morphology; and/or (4)
 266 receptor expression and synaptic transmission. Its effects,
 267 whether transient or permanent, can thus be expected to
 268 have long-term consequences on the shaping and expres-
 269 sion of DA-regulated behaviors. Notably, the consequences
 270 of ELS appear to be different upon the different DAergic
 271 circuits. Perinatal stress seems to decrease steady state
 272 levels of DA in the PFC and to increase it in both the NAcc
 273 and striatum (Boks and El-Khodori 2003). While perinatal
 274 anoxia enhances stress-induced DA release in the NAcc, it
 275 seems to blunt it in the PFC (Brake et al. 1997; 2000),
 276 which strongly suggests different vulnerabilities of the
 277 mesocortical, mesolimbic, and nigrostriatal pathways to the
 278 deleterious effects of stress. A different timing of develop-
 279 ment and maturation of neurons of each circuit or different
 280 intrinsic sensibilities may explain these differences, although
 281 this needs to be further explored.

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

286 ventral part of the mesencephalon. These mesencephalic
 287 neurons are the origin of the so-called mesocortical,
 288 mesolimbic, and nigrostriatal DAergic systems (Fig. 1); a
 289 fourth set of DAergic neurons, less relevant to this article,
 290 follow the tuberoinfundibular pathway to terminate in the
 291 hypothalamo–pituitary unit. Both the mesolimbic and
 292 mesocortical systems arise from the VTA. While the
 293 mesocortical pathway terminates in the cortex, where it
 294 is thought to control cognition and executive functioning,
 295 the mesolimbic projections innervate limbic areas such as
 296 the nucleus accumbens (NAcc), amygdala and hippocampus
 297 and serve in the regulation of memory, motivation,
 298 reward and addiction. Due to their common origins in the
 299 VTA, these two pathways are jointly referred to as the
 300 mesocorticolimbic system, although the activity of each is
 301 subject to regulation by distinct feedback loops. DAergic
 302 neurons that project from the substantia nigra to the
 303 striatum comprise the nigrostriatal system; this pathway is

304 mainly implicated in the initiation and maintenance of
 305 motor behavior. As already mentioned, these midbrain
 306 DAergic neurons are formed during early development,
 307 according to a rostralateral to caudomedial gradient (Bayer
 308 et al. 1995) and their fibers project to terminal fields in the
 309 mesocortical and nigrostriatal areas (Kawano et al. 1995).
 310 All these DAergic systems are thought to be fully mature
 311 and functional by the first few weeks of postnatal life in
 312 both rats (Voorn et al. 1988) and humans (Prakash and
 313 Wurst 2006), although some others have suggested that
 314 this maturation can occur until early adulthood in the PFC
 315 for example (Benes et al. 2000).

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

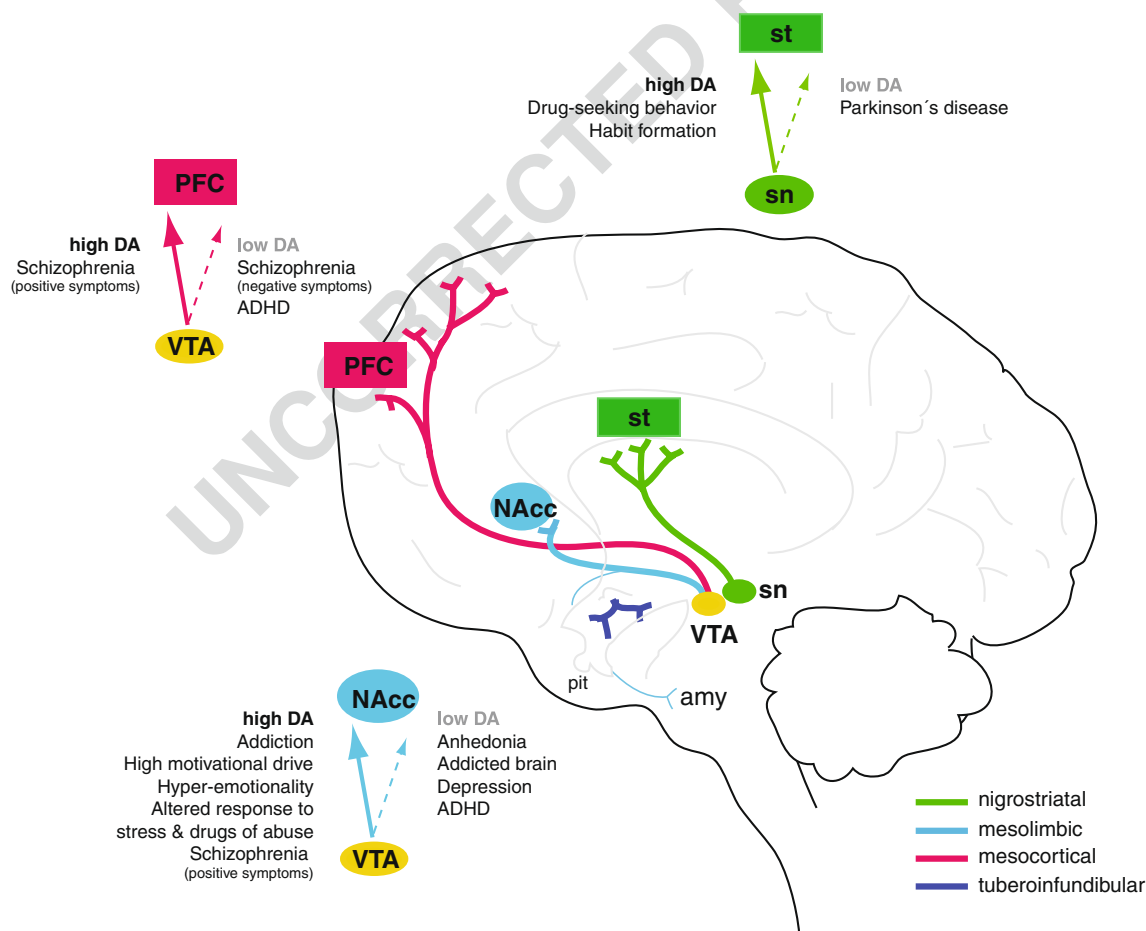


Fig. 1 DAergic pathways of the brain. The mesolimbic and mesocortical pathways arise from the VTA, which lies close to the substantia nigra (*sn*). The mesolimbic pathway projects especially to the nucleus accumbens (*NAcc*), but also to the amygdala (*amy*). The mesocortical pathway projects to the 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.

322 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).

352 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

428 young adulthood has been added to the list of aforemen- 481
 429 tioned neurodevelopmental factors in disease causation 482
 430 (Bayer et al. 1999; Malaspina et al. 2008; Pantelis et al. 483
 431 2003). Indeed, the role of stress in schizophrenia has recently 484
 432 received support from studies in humans (Weber et al. 2008) 485
 433 and animals (Choi et al. 2009). Currently, the leading
 434 hypothesis is that a deficit in DA activity at D1 receptors
 435 in the PFC is responsible for the cognitive impairment and
 436 negative symptoms of schizophrenia, while hyperstimulation
 437 of D2 receptors by subcortical (mesolimbic) DA is respon-
 438 sible for core (“positive”) disease symptoms (hallucinations,
 439 delusions) (Toda and Abi-Dargham 2007).

440 Early life adversity such as lead exposure, drug abuse
 441 (smoking, alcohol, cannabis), low birth weight or premature
 442 birth can increase the risk for developing ADHD, although
 443 genetic factors also play a substantial role on its etiology
 444 (Sullivan and Brake 2003; Swanson et al. 2007). A
 445 dysfunction of DAergic mesocortical (but also mesolimbic
 446 (Russell et al. 1995)) transmission is thought to underlie
 447 ADHD, though the involvement of other neurotransmitters
 448 such as noradrenaline has to be considered (Oades et al.
 449 2005). Briefly, hypofunctioning (especially) of the DAergic
 450 transmission in the right PFC seems to occur in ADHD, and
 451 this is particularly interesting since ELS can induce
 452 lateralized changes on PFC DAergic function (Fride and
 453 Weinstock 1988). Other findings support the involvement
 454 of DA in ADHD: (1) changes in DAT expression were
 455 found in ADHD patients compared to controls (Dougherty
 456 et al. 1999); (2) genetic analysis identified an association
 457 between specific alleles of D4 receptor (Faraone et al. 2001;
 458 Rowe et al. 1998) and of DAT (Waldman et al. 1998) with
 459 ADHD, and (3) the use of methylphenidate which blocks
 460 DA reuptake into the cell by the DAT as the most common
 461 treatment for ADHD.

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

472 It emerges from the above brief overview that ELS may
 473 result in either hyper- or hypoactivity of DAergic systems.
 474 Thus, increased DA transmission in the mesolimbic system
 475 may result in schizophrenia and increased fear, respectively,
 476 whereas reduced DA activity in mesocorticolimbic circuits
 477 may lead to memory (hippocampus and frontal cortex) and
 478 mood (frontal cortex/ventral striatum) deficits (Fig. 1).
 479 Notably, hypoactivity in the hippocampus will likely result
 480 in increased GC secretion which, in turn will exacerbate

neuronal dysfunction and behavioral anomalies. On the
 other hand, stress-induced hypoactivity in the mesocortico-
 limbic 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

488 Despite their diverse chemical structures, cellular mecha- 488
 489 nisms of action and physiological and behavioral manifes- 489
 490 tations, all drugs of abuse share a common property: they 490
 491 all act as positive reinforcers and, as a consequence, induce 491
 492 addiction. Increased DA release in the NAcc characterizes 492
 493 drug reinforcement, but also other consumatory behaviors 493
 494 such as sex and food; thus the VTA-NAcc pathway is 494
 495 appropriately also known as the “reward pathway” (Piazza 495
 496 and Le Moal 1996). Subjective feelings of “pleasure” or 496
 497 hedonia after consummation are experienced as a result of 497
 498 parallel activation of mesocortical DAergic circuits. Though 498
 499 traditionally DA is seen as responsible for the “liking” part 499
 500 of a reward, more recently it has been suggested that DA is 500
 501 not essential/sufficient to mediate changes in hedonic 501
 502 behavior. In fact, DA seems to contribute substantially for 502
 503 incentive salience, i.e., the “wanting” part of the process 503
 504 rather than the “liking” part (Berridge 2007). Nevertheless, 504
 505 one way or another, DAergic transmission is certainly 505
 506 playing a vital role in the rewarding process. Perusal of the 506
 507 literature indicates that an apparently intricately-regulated 507
 508 balance between hypo- and hyper-DAergic states underlies 508
 509 an individual’s cycles of drug-seeking behavior and abuse. 509
 510 Thus, hyper-DAergic states seem to enhance the motiva- 510
 511 tional or rewarding properties of drugs of abuse and hypo- 511
 512 DAergic states appear to enhance drug-seeking behavior in 512
 513 parallel with reductions in the perceived motivational 513
 514 impact of “natural” rewards such as food and sex (Diana 514
 515 et al. 1998; Diana et al. 1993; Melis et al. 2005; Parsons et 515
 516 al. 1991).

517 In the context of this review, it is interesting to note that 517
 518 stress or GC in adulthood enhance DA release in the NAcc 518
 519 (Kalivas and Duffy 1995; Rouge-Pont et al. 1998; 519
 520 Takahashi et al. 1998; Thierry et al. 1976) and increase 520
 521 the strength of excitatory synapses on mesencephalic DA 521
 522 neurons (Saal et al. 2003), while inducing similar patterns 522
 523 of dendritic organization in the NAcc (Liston et al. 2006; 523
 524 Robinson et al. 2001; Robinson and Kolb 1999). Drugs of 524
 525 abuse and stress display other common biobehavioral 525
 526 features: while repeated exposure to the same (Kalivas 526
 527 and Stewart 1991) or novel stressors (Dallman et al. 1994) 527
 528 leads to “facilitation” or “sensitization” of behavioral 528
 529 responses, stress as well as drugs of abuse (Robinson and 529
 530 Becker 1986; Sorg and Kalivas 1991; Stewart and Badiani 530

531 1993) are accompanied by augmented DA release in the
532 NAcc (Doherty and Gratton 1992; Kalivas and Stewart
533 1991). Several other lines of evidence derived from animal
534 studies suggest that stress and GC may act, like drugs of
535 abuse, to induce positive reinforcement: (1) GC facilitate
536 the psychomotor stimulant effects of cocaine, amphetamine
537 and morphine (Cools 1991; Marinelli et al. 1994); (2)
538 depletion of GC by adrenalectomy reduces drug and
539 alcohol consumption (Fahlke et al. 1994; Marinelli and
540 Piazza 2002; Marinelli et al. 1997a; 1997b); (3) GC levels
541 before drug self-administration are positively correlated
542 with the extent of low-dose self-administration of cocaine
543 (Goeders and Guerin 1994; Piazza et al. 1991); and (4)
544 naive rats self-administer GC in a dose-related manner
545 (Piazza et al. 1993).

546 Addiction is determined by a number of factors other
547 than the intrinsic properties of a given drug. In an
548 interesting series of studies aimed at understanding indi-
549 vidual differences in predisposition to drug abuse, Piazza
550 and colleagues found that the liability of rats to self-
551 administer drugs can be predicted by the response of
552 mesolimbic DAergic neurons to stress; specifically, animals
553 that were more sensitive to the DA-releasing actions of
554 stress were more likely to display addictive behavior
555 (Piazza and Le Moal 1996; Piazza et al. 1991). Poly-
556 morphisms in the human DA receptor 2 (Blum et al. 1990;
557 Noble 2000) and DA receptor 1 (Batel et al. 2008; Huang et
558 al. 2008) have been associated with increased propensity to
559 alcohol and other substances of abuse, gambling, and
560 compulsive shopping; however, there is no information
561 available with respect to the physiological responses of the
562 affected individuals to stressful stimuli. Val158Met poly-
563 morphism in catechol-*O*-methyltransferase gene, which is
564 involved in DA degradation, has been associated with
565 schizophrenia, bipolar disorder, and also with substance
566 abuse, although some other studies have failed to prove so
567 (Hosak 2007). Exposure to both, drugs with abuse potential
568 and stress trigger neuroadaptive changes in DAergic
569 circuits that ultimately determine neurochemical and be-
570 havioral responses. This indicates that the activities of
571 addiction-related DAergic pathways are subject to program-
572 ming by lifetime experiences, with the final neurochemical
573 and behavioral phenotype reflecting both genetics and
574 experiential history.

575 Early life adversity, i.e., during the ontogeny of meso-
576 corticolimbic DAergic systems, has been repeatedly shown to
577 induce addiction to a variety of drugs of abuse in adult
578 animals; a few examples from the literature follow: (1)
579 exposure of dams to restraint stress leads to persistent
580 behavioral and neurobiological alterations that are associated
581 with increased consumption of psychostimulants in the adult
582 offspring (Kippin et al. 2008); (2) animals stressed during
583 prenatal life display earlier sensitization to the behavioral

584 effects of amphetamine, although their motor responses to 584
585 the drug do not differ from those of non-stressed animals 585
586 (Henry et al. 1995); (3) separation of pups from their 586
587 mothers and/or littermates during the early postnatal period, 587
588 a procedure that leads to hypersecretion of GC (Ladd et al. 588
589 2000; Liu et al. 1997; Mesquita et al. 2007), advances the 589
590 time of acquisition of cocaine self-administration (Moffett et 590
591 al. 2006) and enhances cocaine-induced locomotor activity 591
592 as well as behavioral sensitization (Brake et al. 2004; 592
593 Kikusui et al. 2005; Li et al. 2003); and (4) MS stress also 593
594 increases alcohol and drug consumption during adulthood 594
595 although handling or brief MS—a manipulation that results in 595
596 reduced GC secretion and responses to stress (de Kloet et al. 596
597 1996; Levine 1967)—decreases voluntary ethanol intake 597
598 (Huot et al. 2001; Ploj et al. 2003). Though human studies 598
599 are sparse, it has been shown that childhood adversity is 599
600 associated with blunted subjective responses to reward- 600
601 predicting cues as well as dysfunction in left basal ganglia 601
602 regions implicated in reward-related learning and motivation 602
603 (Dillon et al. 2009), suggesting that in humans ELS can also 603
604 change the impact of a reward. 604

605 The above examples illustrate the impact that ELS can 605
606 have on the development of addictive behavior and 606
607 reinforce the view that the neuronal circuits involved in 607
608 the regulation of such behavior are particularly vulnera- 608
609 ble to programming by stress and GC during the 609
610 prenatal, perinatal, and early postnatal periods. Part of 610
611 these effects are, as already mentioned, mediated by 611
612 stress and GC participating in the regulation of the birth 612
613 and maturation and DAergic cells in the mesolimbic 613
614 system (Kawamura et al. 2006; Leao et al. 2007). We also 614
615 noted that the adult progeny of dams stressed during 615
616 gestation have significantly fewer TH-positive (DAergic) 616
617 fibers of the NAcc (Leao et al. 2007). Interestingly, these 617
618 presumably hypo-DAergic animals were recently found to 618
619 have a greater propensity for developing drug-seeking 619
620 behaviors (Leão, Rodrigues et al., unpublished observations). 620
621 The above findings may be explained, at least partly, in 621
622 terms of hypersensitivity to the DA-releasing effects of drugs 622
623 of abuse, evidenced by the increased release of DA in 623
624 response to amphetamine or cocaine in rats that have either 624
625 experienced prenatal stress (Kippin et al. 2008; Silvagni et al. 625
626 2008) or maternal deprivation stress in the first postnatal 626
627 days (Hall et al. 1999). 627

628 Finally, alterations in the thresholds required for activa- 628
629 tion of DA type-1 (D1) and type-2 (D2) receptors by DA 629
630 (Volkow et al. 2004) could represent a potential mechanism 630
631 through which ELS causes drug-seeking behavior and 631
632 ultimately, addiction. One hypothetical model predicts that 632
633 the ratio of D1 to D2 receptors in the NAcc determines the 633
634 sensitivity to “natural rewards” vs. the proclivity to “seek 634
635 for pleasure” through drug abuse (Volkow et al. 2004). 635
636 Earlier studies in rats described late gestational stress- 636

637 induced increases in the expression and ligand-binding
 638 capacity of D2 receptors in the frontal cortex, hippocampus,
 639 and core of the NAcc (Berger et al. 2002), with concom-
 640 itant decreases in the number of D1 receptors in the NAcc.
 641 More recently, we observed that the offspring of mothers
 642 exposed to exogenous GC in the last trimester of gestation,
 643 display diminished DA levels in the NAcc and other
 644 mesolimbic structures, an altered D1/D2 ratio and, interest-
 645 ingly, proneness to addictive behaviors (Leão, Rodrigues et
 646 al., unpublished observations).

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

659 **A new player in addiction: the nigrostriatal DAergic**
 660 **pathway?**

661 As recently reviewed by Wise (2009), the nigrostriatal
 662 DAergic system, best known for its role in motor control
 663 and Parkinson’s disease pathology, also seems to play an
 664 important role in addictive disorders. First hints were
 665 provided by the observations that electrical stimulation of
 666 nigrostriatal DAergic cells and terminal fields produced
 667 rewarding effects (Crow 1972; Prado-Alcala and Wise
 668 1984; Wise 1981) and that selective lesions of the
 669 nigrostriatal pathway attenuated drug self-administration
 670 (Glick et al. 1975; Linsman 1976). Those early studies
 671 have been backed up by the results of further experimen-
 672 tation (Suto et al. 2004), including the demonstration that
 673 intra-nigral infusions of D1 receptor antagonists reduce
 674 drug self-administration (Quinlan et al. 2004).

675 Current views suggest that the contributions of the
 676 mesolimbic and nigrostriatal DAergic systems to the devel-
 677 opment of addiction are distinctly separated in time. Thus,
 678 whereas the mesolimbic pathway (especially the NAcc core)
 679 is responsible for the rewarding effects of drugs during the
 680 initial phases of addiction, the nigrostriatal system assumes an
 681 increasingly important role at later stages as drug consump-
 682 tion increases (Everitt et al. 2008; Everitt and Robbins 2005;
 683 Wise 2009). The NAcc core is important not only for the
 684 rewarding effect of drugs of abuse (Wise 2004) but also
 685 mediates the motivational drive or “wanting of a reward”
 686 that underlies drug-craving (Berridge 2007), and assures

efficiency of response-outcome associative learning (Pavlov- 687
 ian conditioning; Yin and Knowlton 2006). However, 688
 second-order protocols of drug reinforcement and pharma- 689
 cological experiments revealed that the dorsal striatum, 690
 rather than the NAcc, is essential for drug-seeking behavior 691
 after repetitive drug exposure (Ito et al. 2000). This 692
 interpretation is consistent with earlier work which showed 693
 that, while dorso-striatal lesions do not affect acquisition of 694
 Pavlovian responses (Taylor and Robbins 1986), infusion of 695
 DAergic antagonists into the dorsal striatum decreases drug- 696
 seeking under second-order drug reinforcement protocols 697
 (Vanderschuren et al. 2005). These findings have led to the 698
 concept that repetitive exposure to drugs of abuse evolve 699
 from being goal-directed behaviors into habit-based actions 700
 (Everitt et al. 2008; Everitt and Robbins 2005; Wise 2009). 701
 Self-administration protocols in monkeys have confirmed the 702
 progressive shift from goal-directed (Pavlovian) behaviors 703
 (facilitated by the NAcc in cooperation with associative 704
 cortico-basal ganglia networks) to habit-based (instrumental) 705
 actions that depend on the dorsal striatum (in particular, the 706
 dorso-lateral striatum, an integral component of the sensori- 707
 motor cortico-basal ganglia pathway (Porrino et al. 2004)). 708

The new knowledge concerning the contribution of the 709
 nigrostriatal DAergic pathway in drug addiction has been 710
 now extended to provide further new insights into how 711
 stress increases vulnerability to drug abuse behavior. 712
 Functional imaging studies in cocaine addicts have revealed 713
 a positive correlation between activation of the dorsal 714
 striatum by stress and the degree of cocaine craving (Sinha 715
 et al. 2005), and our own studies have demonstrated that 716
 stress promotes habit-based decisions in rats by increasing 717
 activation of the sensorimotor cortico-basal ganglia path- 718
 way (Dias-Ferreira et al. 2009); the latter results are 719
 reminiscent of the effects of repetitive drug administration. 720

Albeit several studies have shown that ELS can affect 721
 the mesolimbic circuit, the consequences in the nigrostriatal 722
 circuit remain poorly studied and understood. Prenatal DEX 723
 exposure increases TH+cell numbers in the substantia 724
 nigra, demonstrating that this region can be profoundly 725
 affected in terms of DAergic transmission (McArthur et al. 726
 2005). Furthermore, it was shown that ELS can make 727
 dopamine neurons from the nigrostriatal pathway to 728
 become more susceptible to subsequent insults later in life 729
 (Pienaar et al. 2008). Nonetheless, due to the paucity of 730
 studies, the direct effect(s) of ELS in the development/ 731
 maturation of this circuit and its relevance for addiction for 732
 example, remains to be determined. 733

Future perspectives 734

The available literature, in a rather fragmented way, suggests 735
 an association between ELS, DA transmission, and mental 736

737 illness. Yet, it remains to be answer if the DAergic dysfunction
 738 is causal, or merely a consequence, of ELS and in several of
 739 the psychiatric conditions linked to ELS. Part of the problem
 740 relies on “snapshot approach” that is commonly used in the
 741 available studies that precludes the understanding of the
 742 dynamics of the insult-response-adaptation process. Thus, we
 743 believe that one of the priorities in the field should be to
 744 perform longitudinal studies that establish a direct link
 745 between altered DAergic transmission and specific endophe-
 746 notypes for each of the pathological conditions in which ELS
 747 is implicated. In parallel, a longitudinal multimodal charac-
 748 terization of ELS exposure in the mesolimbic, mesocortical, or
 749 nigrostriatal DAergic pathways is needed. If this is achieved,
 750 ultimately, we could determine what the windows of
 751 vulnerability of each of these DAergic pathways are and
 752 which is more affected in each type of ELS. Furthermore, it
 753 could help us understand the long-term impact, and the
 754 adaptations, of the distinct DA pathways in neuropsychiatric
 755 conditions in which ELS is implicated. As an example, for
 756 addiction studies, this integrated approach would allow for a
 757 better insight on the role of different DA pathways throughout
 758 the different phases of addictive behavior. Moreover, this
 759 would give insights on how neurons in each of these pathways
 760 respond to drugs of abuse and/or stress in both animal models
 761 of ELS and human subjects and how these can be therapeu-
 762 tically modulated. Importantly, this approach is useful and
 763 applicable to many neuropsychiatric conditions.

764 **Conclusions**

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

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