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PERSPECTIVE

The role of stress in the pathophysiology of the dopaminergic system

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In this review, we will examine the most recent preclinical evidence in support of the fact that both acute and chronic stress may have a detrimental impact on the normal function of the dopaminergic system. In recent decades, the term stress has changed its meaning from that of a 'non-specific body response' to a 'monitoring system of internal and external cues'; that is a modality of reaction of the mammalian central nervous system (CNS) which is critical to the adaptation of the organism to its environment. Compelling results have demonstrated that the dopaminergic system is important not only for hedonic impact or reward learning but also, in a broader sense, for reactivity to perturbation in environmental conditions, for selective information processing, and for general emotional responses, which are essential functions in the ability (or failure) to cope with the external world. In this, stress directly influences several basic behaviors which are mediated by the dopaminergic system such as locomotor activity, sexual activity, appetite, and cross sensitization with drugs of abuse. Studies using rat lines which are genetically different in dopamine (DA) physiology, have shown that even small alterations in the birth procedure or early life stress events may contribute to the pathophysiology of psychiatric disorders—in particular those involving central DA dysfunction—and may cause depression or psychotic derangement in the offspring. Finally, the fact that the dopaminergic system after stress responds, preferentially, in the medial prefrontal cortex (MFC), is thought to serve, in humans, as a protection against positive psychotic symptoms, since the increased DA activity in the MFC suppresses limbic DA transmission. However, excessive MFC dopaminergic activity has a negative impact on the cognitive functions of primates, making them unable to select and process significant environmental stimuli. Thus it appears that a critical range of DA turnover is necessary for optimal cognitive functioning after stress, in the response of the CNS to ever-changing environmental demands. *Molecular Psychiatry* (2000) **5,** 14–21.

Keywords: dopamine; HPA; rats; medial prefrontal cortex; nucleus accumbens

Introduction

In 1973, Hans Selye defined stress as 'the non-specific response of the body to any demands made upon it',[1] while more recent definitions have tended to see the stress response in terms of being both a survival mechanism and an indicator of internal and external cues.[2] The word 'stress', in the meaning we intend to use in the present review, describes a general reaction of the mammalian central nervous system (CNS) which plays a vital role in the way an organism monitors internal conditions, as well as conditions in the world around it, in order to attempt to survive.

Environmental or pharmacological manipulations of dopaminergic transmission are able to modify basic forms of behavior present in nature and linked to the survival of the individual and the species. Disruption of dopaminergic transmission will affect behavior which is related to the ability to 'feel' the environment and to take decisions based upon those sensations, which will affect the emotional status of the individual; that is, survival through the attribution of incentive salience to significant environmental stimuli and contextual reward/avoidance learning.[3,4] This unique ability has established dopamine (DA), throughout evolution, as the principal neurotransmitter of *motivated action*, in the sense of physical and psychological movement toward 'pleasure' or away from 'pain'.[5–7] In this, the response of the dopaminergic system is neither homogenous nor generalized, and numerous results suggest that mesoprefrontal cortex (MFC) DA neurons are selectively activated by sudden changes in environmental conditions whether expected or not, and that the activation of the A10 cell body site precedes that of the terminal fields.[8] Interestingly, the nucleus accumbens (NAc) DA reaction to internal or external perturbations is dampened by the concurrent activation of MFC DA neurons; an action mediated, at least in part, by D1 receptors in the MFC.[9] When 6-OHDA lesions are produced in the prefrontal cortex, mild footshock results in a significant increase in the concentration of DOPAC in the NAc. More pre-

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cisely, depletion of DA in the MFC potentiates the stress-induced increase in extracellular DA in the NAc shell, confirming that mesocortical DA neurons may influence stress-evoked DA efflux in this specific area.[10,11]

There is no corresponding increase, however, in the striatum, showing that disruption of the prefrontal DA innervation results in an enhanced responsiveness to stress that is preferential for the mesolimbic DA system.

Stimuli that increase the release of DA in the MFC or NAc, whether natural (water, food, and sex) or artificial (produced by means of drugs or electricity), can be heavily affected by stress. The exposure to acute inescapable shock interferes with the capacity of the animal to consume a highly palatable diet. The magnitude and duration of the response varies across different strains of mice,[12] suggesting that a genetic component is important for encoding this reaction modality of the brain DA system.

The sexual behavior of male rats is also impaired by long-term stress, which leads to a decrease in the activity of DA neurons.[13] Prenatally stressed rat males do not exhibit copulation during sexual behavior tests, and no significant changes in DA release are seen during exposure to estrous females, suggesting a deficit in DA neurotransmission in the Nac.[14] Acute injection of the mixed DA D1/D2 receptor agonist apomorphine significantly increases both the incidence and the frequency of copulatory elements (mounting and intromission) in a dose-dependent manner. The combination of L-dopa with carbidopa, a dopa decarboxylase inhibitor, also significantly increases copulatory behavior, confirming that dopaminergic mechanisms are involved in copulatory disorders induced by social stress.[15]

In rats, subtle alterations in the birth procedure, able to produce a period of anoxia in the fetus, may be sufficient to increase the sensitivity of mesolimbic DA neurons to the effects of repeated stress in the adult animal. This offers support to the idea that birth complications may contribute to the pathophysiology of psychiatric disorders—in particular those that involve central DA dysfunction[16]—and may help to explain the interface between genetic and environmental determinants that are thought to cause permanent changes in those areas of the dopaminergic system[17] which are important for mood swings, drug abuse (see below) and psychotic decompensation in the offspring.

Repeated stress (for 8 days) reduces the basal locomotor activity of rats, prolongs immobility time in Porsolt's despair test, and decreases the utilization of DA in the brain. These effects can be blocked by imipramine given once a day for 8 days,[18] but the acute administration of DA D1 or D2 receptor antagonists reverses such improvement.[19] Chronic mild stress (CMS) for 16 days reduces the number of fighting attacks, and this behaviour is also restored in stressed rats treated chronically (for 14 days) with antidepressants; and again such restoration is blocked by pretreatment with DA receptor blockers.[20] Fourteen days of CMS reduces the consumption of sucrose and normal behavior is restored by chronic (>6 weeks) treatment with either classic tricyclic antidepressants,[21] atypical antidepressants,[22] or, more recently, with the DA agonists quinpirole,[23,24] or the autoreceptor blocker amisulpride.[25]

The fine tuning of DA extracellular concentration in the MFC seems to be essential for the decision-taking protocols of the CNS, since excessive DA activity is detrimental to the spatial working memory functions of the MFC in the rat and the monkey.[26] This supports the idea of a critical range of DA turnover for optimal prefrontal cortical cognitive functioning, with reduced or excessive DA turnover leading to cognitive impairment. Several data point to ventral tegmental area (VTA) projections,[27] DA receptors,[28] and a loss of inhibitory tone on VTA DA cells[29] as important regulatory sites for maintaining superior cognitive functions. The increased ability to remove DA in chronically stressed animals has also indicated that altered DA clearance may serve as an adaptive mechanism in the MFC.[30] It has been further suggested that increased D1 receptor stimulation during stress may serve to take the MFC 'off-line', in order to allow posterior cortical and subcortical structures to regulate more 'primitive' forms of behavior.[31] Since dopaminergic innervation of the MFC is able to regulate the activity of subcortical DA innervations, disruption of the MFC DA fibers may result in the altered biochemical responsiveness of the DA subcortical innervations.[32]

Also of clinical relevance is the fact that when rats are psychologically stressed by being acutely exposed to the emotional responses of footshocked rats, but are themselves prevented from receiving footshock, significant increases in both DOPAC and homovanillic (HVA) levels in the MFC—but not in other DA terminal fields—is observed, while the levels of noradrenaline, serotonin and 5-hydroxyindoleacetic acid are unaffected in all brain regions examined.

In humans, the balance between cortical and subcortical dopaminergic activity, may serve as a protection against psychotic decompensation from chronic endogenous or exogenous insult.[33] However, the failure of this coping mechanism may well contribute to the vulnerability of the MFC in many neuropsychiatric disorders related to the stress response.[34]

In short, there is enough preclinical evidence to support the view that stress, in both its acute and chronic form, may have a negative impact on the normal physiology of the dopaminergic system. In this review we will summarize biochemical, pharmacological and behavioral preclinical data from different laboratories, which have recognized the importance of DA for the control of complex behaviors in response to variations in environmental conditions. This is a much more complete role of DA than that which Paul MacLean originally defined as 'the vital neurotransmitter that brings the total energies of the organism into play'.[35]

Stress, dopamine and specific brain areas (a clue for selective information processing?)

Several studies sustain the view that not only stressful events, but even mild environmental changes which evoke emotional arousal (whether aversive or non-aversive), are accompanied by increased DA extracellular concentration in the MFC, and only to a minor extent in the limbic and striatal areas.[36] The forebrain DA projections are differentially regulated during ongoing behavior; the mesocortical dopaminergic projection to the MFC being in general more responsive to stressful and rewarding stimuli than those innervating the striatum (NAc and caudate putamen).[37] This activation is very selective, since molecular studies have shown that thirty minutes of restraint increase Fos protein in DA neurons projecting to the MFC, but not in those projecting to the NAc.[38] Altered accumbens and cortical extracellular DA concentrations during stress (social threat) are not secondary to motor activation, but instead reflect increased attention to the provocative stimulus or attempts by the intruder to 'cope' with the stimulus,[39] and therefore indicate that the dopaminergic system has the ability to select, discriminate and react to psychological or physical stimuli, which is independent of aspecific motor activation. Tail shock, for instance, increases DA in the striatal extracellular fluid of striatal lesioned 6-OHDA rats even when the animals are akinetic, demonstrating that residual nigrostriatal DA neurons are still responsive to stress,[39] through a mechanism that bypasses the pure capacity to set the body in motion.

In this sense the magnitude and site specificity of the dopaminergic response may depend on the nature of the stimulus,[40] suggesting a selective capacity to process the information coming from the individual's surroundings. Such selectivity has also been shown on different sides of the MFC as they are successively activated as stressors are prolonged. The effects of variations in the duration of a restraint stressor on region and side-dependent alterations in DA utilization confirm that the largest effects occur in the MFC, and lesser effects in the basal ganglia, changing according to the time of restraint exposure.[41] Others have hypothesized that the biphasic (ie rising and falling) alteration of DA transmission in the mesolimbic system could suggest that the initial increase of DA release represents an arousal response, while the subsequent decrease in DA release may be related to coping failure.[42]

The ability of the DA system to discriminate and process neural representations of change-related stimuli is also indicated by the response to different types of stress, since loose restraint induces acutely significant increases in DA release in the anterior MFC and NAc septum (NAS), but the increased DA levels return to control values if stress is chronically applied. The more widespread activation of DA after more severe types of stress might thus relate to behavioral changes which reflect the augmentation of fear.[43]

The fact that regional variations could underlie the neuronal basis for selective information processing is also indicated by the significant differences that exist between the NAc core and shell in the basal DA metabolism, and by their response to environmental challenges.[44] The ventral striatum projection target (NAc shell) of the prefrontal cortical region is more responsive to stress,[45] and when a microdialysis probe is placed in either the shell or core compartment of the NAc, and rats are exposed to mild footshock, extracellular DA levels increase only in the shell of the NAc.[46]

Finally, the role of previous experience should be taken into consideration when examining the response to subsequent stress. The first exposure to swim stress, for instance, while not causing dramatic changes in DA release, may sensitize the MFC to subsequent swim stress.[47] Cross sensitization between different types of stress has also been reported. Tail shock elicits a greater increase in DA efflux with respect to baseline values in rats which have previously been exposed to cold than in naïve rats; once again this increase is observed only in the MFC, and not in the NAc or striatum.[48]

Discriminating ability is also evident in the capacity of the DA system to react differently to unrelated types of stress. Cold restraint activates the DA metabolism in the MFC, NAS and striatum, while restraint activates the DA metabolism in the MFC alone.[49]

Stress, genetic background and dopamine receptors (a switch for reactivity to perturbations?)

The alterations in the way the dopaminergic system develops and functions start early in life, some studies suggesting that it might even have strong genetic components. Several results invite speculation that one of the key factors in the expression of dopaminergic system genetic variability (and vulnerability) in response to stress-related stimuli could be at the level of DA turnover and/or D2/D3 receptors.

In the MFC and NAc exposure to an acute stressor induces an increase of 3,4-dihydroxy phenylacetic (DOPAC) accumulation along with pronounced reductions of DA in some mice strains, while in others these variations are less pronounced or entirely absent,[50] suggesting a close relationship between genetic or epigenetic variations in the sensitivity of the mesolimbic system and the behavioral alterations which are produced by acute or chronic stress.[51]

In mice, repeated stressful experiences lead to hyposensitivity of DA D2 presynaptic receptors in the DBA/2Js strain, while producing a sensitization of the same receptors (possibly accompanied by a down-regulation of postsynaptic DA D2 receptors) in the C57BL/6J strain.[52] When submitted to ten daily restraint stress sessions DBA/2Js mice present a decrease in D2 receptor density, but show no change in D1 receptor density in the NAS.[53] In addition, DBA/2J mice become sensitized to the stimulatory effect of amphetamine on locomotion, while C57BL/6J mice do not.[54]

The direct involvement of DA receptors in the reaction to (and memory of) stressful conditions is shown when mice are replaced in the same environment in which they have previously received an electric footshock. In this case the activation of both DA D1 and D2 receptors seems necessary in order to attenuate the conditioned, fear and stress-induced, motor suppression.[55]

Epigenetic components may also be able to permanently alter the response to stress. Prenatal stress, for instance, has been found to produce the following alterations in adult rat offspring: (i) a significant increase in D2 receptor binding in the NAc; and (ii) a significant decrease in D3 receptor binding in both the shell and the core of the NAc.[56] Variations in gene expression or post translational modifications may account for the changes in the density and affinity of D2 receptors that have been found in rats exposed to 2-h restraint stress,[57] hyperthermia or turpentine treatment.[58]

CMS causes a decrease in the number of D2 receptors, but not affinity, in the rat limbic forebrain (nor in the striatum), which is completely reversed by chronic imipramine.[59] Changes in D2 receptor function in the NAc produced after CMS are similar to those observed after footshock stress.[60]

These conditions seem to be preserved during evolution up to the levels of primates. In adult male cynomolgus macaques, the effects of chronic social stress and social rank show long-term selective reductions in serotonergic activity in the MFC,[61] which is thought *per se* to influence the dopaminergic tone in this region,[62] and which decreases D2 receptor binding in socially subordinate adult females.[63]

Stress, dopamine and other neurotransmitters (the gates for emotional responses?)

Other neuronal circuits most likely recruited during and immediately after the hypothalamo-pituitary-adrenal (HPA) axis activation should be considered in order to fully understand the complete response of the dopaminergic system in modulating and controlling emotional behavior in response to ever-changing environmental demands. When neonatal lesions of the VTA are performed, it is found that even moderate lesions of the DA system may alter the normal hormonal response to stress, indicating that the dopaminergic system may have a direct influence on the HPA axis.[64]

The fact that in laboratory animals the effect of early stressful experiences on brain DA functioning may not be evident in basal conditions, but can only be revealed under environmental pressure which evokes anxiety and/or fear,[65] has suggested a possible role for other transmitter systems which may give an 'emotional connotation' to stress.

Two neuronal 'gates' should be regarded as system modulators of the MFC response to stress: one is the ventral hippocampus, which attributes significance to environmental cues; the other is the hypothalamus, which regulates the activity of cortical systems involved in sensations related to the above cues. Both systems participate in the dopaminergic MFC cognitive elaboration of the stressor and subsequent reaction response, either increasing exploration (by means of curiosity and reward) or decreasing it (through fear and aversion).

When neonatal ibotenic acid lesions are produced in the ventral hippocampus, repeated intraperitoneal saline injections attenuate DA release in the MFC, NAc and striatum, while chronic haloperidol augments DA release in the MFC of lesioned animals compared to controls.[66] This suggests that the ventral hippocampus influences the functioning of midbrain DA systems during environmental and pharmacological challenges in different ways.

GABA

Recent results have implicated hypothalamic GABA neurotransmission as a 'gating' activity of cortical systems which are involved in the sensation of, and/or response to, stressors. The microinfusion of bicuculline methiodide into the medial hypothalamus of freely moving, handling-habituated rats, leads to rapid increases in MFC DA utilization, resembling that identified following restraint-induced stress.[67]

Evidence that the activity of mesocortical dopaminergic pathways is altered in an opposite manner by drugs that either inhibit or enhance the GABAergic transmission indicate that GABA could have a functional role in the regulation of dopaminergic neurons in the rat MFC during stress.[68] Accordingly, the endogenous levels of DA in the rat MFC have been found to be significantly increased by both zopiclone and diazepam; an effect antagonized by Ro 15–1788, suggesting that it is mediated by specific benzodiazepine receptors.[69]

The increase of DOPAC levels in the MFC 30 min after psychological stress is attenuated by diazepam, and this attenuating effect is also antagonized by Ro 15–1788.[70] Intraventricular administration of the neuroactive steroid 3 alpha-21-dihydroxy-5alpha-pregname-20-one results in a dose-dependent decrease in DA metabolites only in the prefrontal cortex. Moreover, this neuroactive steroid selectively attenuates the stress-induced activation of the MFC DA system.[71] In both naïve rats and rats which have been previously exposed to chronic cold, acute tail pressure elicits an increase in the concentrations of DA in the MFC; diazepam blocks this increase only in the naïve animals. The effects of imidazenil and abecarnil, partial and selective benzodiazepine recognition site agonists, are in part similar to those observed with classical benzodiazepines,[72] showing no effect on basal DA and a complete prevention of stress-induced cortical DA release.[73] These findings have also been confirmed in rats exposed to an environment associated with aversive stimuli footshock.[74]

Excitatory amino acid

Indirect confirmation of the mechanisms by which the MFC may interfere with the response of the limbic system to stress comes from lesion studies. In the neostriatum, stress-induced DA release is thought to be mediated by an action of glutamate on the DA cell body, while stress-induced DA synthesis could be mediated by an action of glutamate on the DA nerve terminal.[75]

The removal of corticofugal glutamatergic neurons from tonic DA inhibition results in a transynaptic alteration in the NAc, in such a way that the DA innervation of the NAc is rendered hyperresponsive to certain environmental perturbations.[30] Systemic administration of the non-competitive antagonist for the N-methyl-D-aspartate (NMDA) receptor complex, dizocilpine (MK-801), blocks the stress-induced rise in DA metabolism in the MFC but not in the NAc; similar results have been obtained with 3-amino-1 hydroxypyrrodilin-2-one (HA-966), an antagonist of the allosteric glycine site of the NMDA receptor, given systemically or injected into the VTA.[76] Pretreatment with HA-966 also completely abolishes the conditioned stress-induced increase in DA utilization in the medial and lateral prefrontal cortices, but not in the NAc.[77] Other results fail to support the hypothesis that the stress-induced increase in extracellular DA in the neostriatum is initiated locally by excitatory amino acids.[78] However, the local perfusion of the AMPA/kainate receptor antagonist blocks the stress-induced increase in DA levels, whereas another NMDA receptor antagonist, 2-amino-5-phosphonopentanoic acid (AP5), is not able to alter this response significantly. This indicates that the effect of stress on DA release in the prefrontal cortex could be differentially regulated by the NMDA receptor.[79] Since local application of the kainate/AMPA receptor antagonist 6,7 dinitroquinoxaline-2,3 dione (DNQX) fails to alter the NAc DA stress response, relevant populations of NMDA receptors could be not located on NAc DA terminals, and suggests instead an action mediated by NMDA receptors located on NAc neurons that feed back, directly or indirectly, to cell bodies of the mesocorticolimbic DA system.[80] Other types of stress (eg intraperitoneal saline injections) and other means of lesioning the MFC (eg ibotenic acid), confirm that after stress not only are the levels of mesolimbic DA and its metabolites elevated, but also that this effect will persist for up to 7 days.[81]

Recently, the mutual interactions of these two neuronal gates were demonstrated by showing that antagonists at the glycine/NMDA receptor complex share similarities with benzodiazepine/GABA(A) receptor agonists.

DA metabolism, as reflected by the concentration of DOPAC in the MFC, significantly increases following acute immobilization stress or systemic administration of the benzodiazepine/GABA(A) receptor inverse agonist methyl-6, 7-dimethoxy-4-ethyl-beta-carboline-3 carboxylate (DMCM). The response to both stress and DMCM is attenuated by pretreatment of rats with HA-966, a low efficacy partial agonist, and 7-chloro-4-hydroxy-3-(3-phenoxy) phenyl-2-(H) quinoline (L-701,324), a high affinity, full antagonist at the glycine/NMDA receptor.[82]

Stress and drug abuse (a model for dopamine/corticosteroid interactions?)

Research into drug abuse has focused on the way in which the interaction between stress, corticosteroids, and mesencephalic dopaminergic neurons affects the ability to discriminate significant from less significant environmental cues. It seems that all these components are organized in a 'pathophysiological chain of events', determining vulnerability to the maladaptive use of drugs.[83] There is also evidence that certain stress-induced psychopathological conditions are accompanied by a dysfunction of both the dopaminergic systems and the HPA axis, although the relationship between these two systems is still unclear. Studies using rat lines which have been genetically selected for extreme differences in DA phenotype, as well as rats exposed as infants to the traumatic experience of maternal deprivation, allow the conceptualization of a framework of DA-related psychopathology in relation to genetic predisposition, early life events and stress hormones. During development, exposure to corticosterone and to sensory stimulation has long-lasting consequences for the organization of the stress response system. Factors inherent in the mother-pup interaction are thought to be critical for DA phenotype, corticosterone receptor dynamics, and neuroendocrine regulation in adult life.[84] Exposure of rats to restraint stress during late pregnancy produces offspring with a variety of behavioral and neurobiological alterations, such as long-lasting changes in the HPA axis,[85] increased immobility time in the Porsolt test, and a reduction of the DOPAC/DA index in the NAc,[86] all of which can be considered co-factors in the development of drug addicting behaviors.

Other studies have focused on stress events in order to better understand the vulnerability to addiction that is present in certain individuals.[87] At least in part, sensitization (ie augmentation of psychostimulant-induced motor activity) is thought to result from a long-term change in MFC DA transmission, and may involve a disinhibition of DA neurons;[88] it is logical to infer that any condition that would alter MFC physiology may in turn affect the vulnerability to drug abuse. These components were considered together when sensitization to the increased extracellular concentration of DA induced by cocaine was studied in rats in which corticosterone secretion was either intact or blocked with metyrapone (an inhibitor of corticosterone synthesis); it was found to suppress both the development and the expression of sensitization.[89] Adrenalectomy blocks the cocaine-induced sensitization observed in sham animals, but both sham and adrenalectomized rats demonstrate behavioral sensitization to cocaine, showing that long-term alterations in DA transmission may be an important neurochemical

substrate of stress and psychostimulant-induced sensitization.[90]

The suppression of stress-induced corticosterone secretion abolished 8 days of food restriction-induced sensitization to the locomotor effects of intra-NAc amphetamine and intra-VTA morphine, suggesting that glucocorticoids may control stress-induced sensitization by changing the sensitivity of the mesencephalic dopaminergic transmission to drugs of abuse.[91]

Prenatal stress induces changes in the DA sensitivity of the NAc and in the capacity to develop amphetamine-induced sensitization in adulthood, which is thought to be mediated by an impaired control of corticosterone secretion in prenatally-stressed animals.[92]

When the behavioral and neurochemical cross-sensitization between cocaine and repeated footshock stress was examined in adult animals, it was found that both the cocaine-induced increase in extracellular MFC DA levels and the motor stimulant response to acute cocaine were augmented in shock-pretreated rats.[92,93] The MFC dopaminergic system is also involved in cross-sensitization between D-amphetamine and stress,[94] which does not depend on the length of exposure to stress (acute or chronic) but rather on a sufficient degree of stimulation of both D1 and D2 dopaminergic receptors.[95]

Finally, ethanol has been shown to have different, dose-dependent effects in resting *vs* stressed (immobilized) rats, being able to antagonize stress-induced increases in DA at high doses (ie 2 g kg^{-1} i.p.),[96] while lower doses preferentially blocked the stress-induced increases in DOPAC in the MFC.[97] In mice, the stress emanating from a novel environment may affect not only motor activity *per se*, but also the interaction between dopaminergic antagonists with ethanol.[98]

Interestingly, in humans a specific gene-environment interaction involving cognitive functioning has recently been reported between the TaqI A DA D2 receptor alleles, family stress, and cognitive markers, including visuospatial ability (Benton's Line Orientation) and event-related potentials (P300 amplitude and latency), in preadolescent sons of alcoholic and non-alcoholic fathers.[99]

Conclusions

These complex interactions reported in laboratory animals are of great relevance for the clinician since, for instance, preclinical data suggest a close and significant interplay between stress, antidepressants, drugs of abuse and the physiological integrity of the DA system.

We have attempted to illustrate such complex interactivity between the mesocortical dopaminergic system and stress activation in response to pleasurable, as well as avoidable, experiences. A large body of recent evidence has contributed to the recognition of dopaminergic innervation as an important system for determining reactions to perturbations in environmental conditions, for selective information processing, and for controlling emotional behavior, all of which play an essential role in the ability (or failure) to cope with the external world.

In this context, we feel that the stress axis should no longer be regarded as a 'simple' emergency system (the so called 'fight or flight' response), but more as a constant apparatus for monitoring internal and external stimuli, and which uses the changes in environmental conditions as a regulatory device.

In this respect, such a system would be intended not only for the performance of routine checking, but also to decide upon priorities in order to maintain vital functions, such as drinking, eating and reproduction. These are behavioral correlates of the normal dopaminergic function, and can show significant deficits in both the first expression or exacerbation of many neurological and psychiatric disorders following stress.

References

1 Selye H. The evolution of the stress concept. *Am Sci* 1973; **61**: 692–696.
2 Akil HA, Morano IM. Stress. In: Kupfer D, Bloom F (eds). *Psychopharmacology*, the *Fourth Generation of Progress*. Raven Press: New York, 1995, pp 773–785.
3 Pani L, Gessa GL. Evolution of the dopaminergic system and its relationships with the psychopathology of pleasure. *Int J Clin Pharm Res* 1997; **17**: 55–58.
4 Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Rev* 1998; **28**: 309–369.
5 Wise RA. The brain and reward. In: Liebman J, Cooper SJ (eds). *The Neuropharmacological Basis of Reward*. Oxford University Press: Oxford, 1989, pp 377–424.
6 Fibiger HC, Phillips AG. Role of catecholamine transmitters in reward systems: implications for the neurobiology of affect. In: Oreland E (ed). *Brain Reward Systems and Abuse*. New York Press: New York, 1987, pp 61–74.
7 Blackburn JR, Pfaus JG, Phillips AG. Dopamine functions in appetitive and defensive behaviors. *Progr Neurobiol* 1992; **39**: 247–279.
8 Kaneyuki H, Yokoo H, Tsuda A, Yoshida M, Mizuki Y, Yamada M *et al*. Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: reversal by diazepam. *Brain Res* 1991; **557**: 154–161.
9 Doherty MD, Gratton A. NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. *Synapse* 1997; **26**: 225–234.
10 King D, Zigmond MJ, Finlay JM. Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular dopamine in the nucleus accumbens core and shell. *Neuroscience* 1997; **77**: 141–153.
11 King D, Finlay JM. Loss of dopamine terminals in the medial prefrontal cortex increased the ratio of DOPAC to DA in tissue of the nucleus accumbens shell: role of stress. *Brain Res* 1997; **767**: 192–200.
12 Griffiths J, Shanks N, Anisman H. Strain-specific alterations in consumption of a palatable diet following repeated stressor exposure. *Pharmacol Biochem Behav* 1992; **42**: 219–227.
13 Sato Y, Kumamoto Y. Psychological stress and sexual behavior in male rats. II. Effect of psychological stress on dopamine and its metabolites in the critical brain areas mediating sexual behavior. *Nippon Hinyokika Gakkai Zasshi* 1992; **83**: 212–219.
14 Wang CT, Huang RL, Tai MY, Tsai YF, Peng MT. Dopamine release in the nucleus accumbens during sexual behavior in prenatally stressed adult male rats. *Neurosci Lett* 1995; **200**: 29–32.
15 Sugiura K, Yoshimura H, Yokoyama M. An animal model of copulatory disorder induced by social stress in male mice: effects of apomorphine and L. dopa. *Psychopharmacol Berl* 1997; **133**: 249–255.
16 Brake WG, Noel MB, Boksa P, Gratton A. Influence of perinatal

factors on the nucleus accumbens dopamine response to repeated stress during adulthood: an electrochemical study in the rat. *Neuroscience* 1997; **77**: 1067–1076.
17 Alonso SJ, Navarro E, Rodriguez M. Permanent dopaminergic alterations in the n. accumbens after prenatal stress. *Pharmacol Biochem Behav* 1994; **49**: 353–358.
18 Zebrowska-Lupina I, Stelmasiak M, Porowska A. Stress, induced depression of basal motility: effects of antidepressant drugs. *Pol J Pharmacol Pharm* 1990; **42**: 97–104.
19 Sampson D, Willner P, Muscat R. Reversal of antidepressant action by dopamine antagonists in an animal model of depression. *Psychopharmacol Berl* 1991; **104**: 491–495.
20 Zebrowscka-Lupina I, Ossowska G, Klenk-Majewska B. The influence of antidepressants on aggressive behavior in stressed rats: the role of dopamine. *Pol J Pharmacol Pharm* 1992; **44**: 325–335.
21 Sampson D, Willner P, Muscat R. Reversal of antidepressant action by dopamine antagonists in an animal model of depression. *Psychopharmacol Berl* 1991; **104**: 491–495.
22 Muscat R, Papp M, Willner P. Reversal of stress, induced anhedonia by the atypical antidepressants, fluoxetine and maprotiline. *Psychopharmacol Berl* 1992; **109**: 433–438.
23 Papp M, Willner P, Muscat R. Behavioural sensitization to a dopamine agonist is associated with reversal of stress, induced anhedonia. *Psychopharmacol Berl* 1993; **110**: 159–164.
24 Papp M, Muscat R, Willner P. Subsensitivity to rewarding and locomotor stimulant effects of a dopamine agonist following chronic mild stress. *Psychopharmacol Berl* 1993; **110**: 152–158.
25 Willner P. Pharmacology of anhedonia. *Eur Neuropsychopharmacol* 1995; **5**(suppl 3): 214s–221s.
26 Murphy BL, Arnsten AF, Goldman-Rakic PS, Roth RH. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proc Natl Acad Sci USA* 1996; **93**: 1325–1329.
27 Murphy BL, Arnsten AF, Jentsch JD, Roth RH. Dopamine and spatial working memory in rats and monkeys: pharmacological reversal of stress, induced impairment. *J Neurosci* 1996; **16**: 7768–7775.
28 Steketee JD, Kalivas PW. Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. *J Pharmacol Exp Ther* 1991; **259**: 916–924.
29 Sorg BA, Steketee JD. Mechanisms of cocaine, induced sensitization. *Prog Neuropsychopharmacol Biol Psychiatry* 1992; **16**: 1003–1012.
30 Meiergerd SM, Schenk JO, Sorg BA. Repeated cocaine and stress increase dopamine clearance in the rat medial prefrontal cortex. *Brain Res* 1997; **773**: 203–207.
31 Zahrt J, Taylor JR, Mathew RG, Arnsten AF. Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. *J Neurosci* 1997; **17**: 8528–8535.
32 Deutch AY, Clark WA, Roth RH. Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. *Brain Res* 1990; **521**: 311–315.
33 Friedhoff AJ, Carr KD, Uysal S, Schweitzer J. Repeated inescapable stress produces a neuroleptic-like effect on the conditioned avoidance response. *Neuropsychopharmacology* 1995; **13**: 129–138.
34 Finlay JM, Zigmond MJ. The effect of stress on central dopaminergic neurons: possible clinical implications. *Neurochem Res* 1997; **22**: 1387–1394.
35 MacLean PD. Brain evolution relating to family, play and the separation call. *Arch Gen Psychiatry* 1985; **42**: 405–417.
36 Cenci MA, Kalen P, Mandel RJ, Bjorklund A. Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: a microdialysis study in the rat. *Brain Res* 1992; **581**: 217–228.
37 Cabib S, Puglisi-Allegra S. Stress, depression and the mesolimbic dopamine system. *Psychopharmacol Berl* 1996; **128**: 331–342.
38 Deutch AY, Lee MC, Gillham MH, Cameron DA, Goldstein M, Iadarola MJ. Stress selectively increases fos protein in dopamine neurons innervating the prefrontal cortex. *Cereb Cortex* 1991; **1**: 273–292.
39 Keefe KA, Stricker EM, Zigmond MJ, Abercrombie ED. Environmental stress increases extracellular dopamine in striatum of 6-hydroxydopamine-treated rats: *in vivo* microdialysis studies. *Brain Res* 1990; **527**: 350–353.
40 Tidey JW, Miczek KA. Social defeat stress selectively alters mesocorticolimbic dopamine release: an *in vivo* microdialysis study. *Brain Res* 1996; **721**: 140–149.
41 Carlson JN, Fitzgerald LW, Keller RW Jr, Glick SD. Side and region dependent changes in dopamine activation with various durations of restraint stress. *Brain Res* 1991; **550**: 313–318.
42 Cabib S, Puglisi-Allegra S. Genotype-dependent effects of chronic stress on apomorphine-induced alterations of striatal and mesolimbic dopamine metabolism. *Brain Res* 1991; **542**: 91.
43 Inoue T, Tsuchiya K, Koyama T. Regional changes in dopamine and serotonin activation with various intensity of physical and psychological stress in the rat brain. *Pharmacol Biochem Behav* 1994; **49**: 911–920.
44 Deutch AY, Cameron DS. Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. *Neuroscience* 1992; **46**: 49–56.
45 Deutch AY. Prefrontal cortical dopamine systems and the elaboration of functional corticostriatal circuits: implications for schizophrenia and Parkinson's disease. *J Neural Transm Gen Sect* 1993; **91**: 197–221.
46 Kalivas PW, Duffy P. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. *Brain Res* 1995; **675**: 325–328.
47 Jordan S, Kramer GL, Zukas PK, Petty F. Previous stress increases in vivo biogenic amine response to swim stress. *Neurochem Res* 1994; **19**: 1521–1525.
48 Gresch PJ, Sved AF, Zigmond MJ, Finlay JM. Stress-induced sensitization of dopamine and norepinephrine efflux in medial prefrontal cortex of the rat. *J Neurochem* 1994; **63**: 575–583.
49 Sudha S, Pradhan N. Stress, induced changes in regional monoamine metabolism and behavior in rats. *Physiol Behav* 1995; **57**: 1061–1066.
50 Shanks N, Zalcman S, Zacharko RM, Anisman H. Alterations of central norepinephrine, dopamine and serotonin in several strains of mice following acute stressor exposure. *Pharmacol Biochem Behav* 1991; **38**: 69–75.
51 Puglisi-Allegra S, Kempf E, Cabib S. Role of genotype in the adaptation of the brain dopamine system to stress. *Neurosci Biobehav Rev* 1990; **14**: 523–528.
52 Cabib S, Puglisi-Allegra S. Genotype-dependent effects of chronic stress on apomorphine-induced alterations of striatal and mesolimbic dopamine metabolism. *Brain Res* 1991; **542**: 91–96.
53 Puglisi-Allegra S, Kempf E, Schleef C, Cabib S. Repeated stressful experiences differently affect brain dopamine receptor subtypes. *Life Sci* 1991; **48**: 1263–1268.
54 Badiani A, Cabib S, Puglisi-Allegra S. Chronic stress induces strain-dependent sensitization to the behavioral effects of amphetamine in the mouse. *Pharmacol Biochem Behav* 1992; **43**: 53–60.
55 Kamei H, Kameyama T, Nabeshima T. Activation of both dopamine D1 and D2 receptors necessary for amelioration of conditioned fear stress. *Eur J Pharmacol* 1995; **273**: 229–333.
56 Henry C, Guegant G, Cador M, Arnauld E, Arsaut J, Le-Moal M *et al*. Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. *Brain Res* 1995; **685**: 179–186.
57 Kiyatkin EA, Belyi VP, Rusakov DYU, Maksimov VV, Pankratova NV, Rozhanets VV. Long-term changes of striatal D-2 receptors in rats chronically exposed to morphine under aversive life conditions. *Int J Neurosci* 1991; **58**: 55–61.
58 Tomic M, Joksimovic J. Glucocorticoid status affects the response of rat striatal dopamine D2 receptors to hyperthermia and turpentine treatment. *Endocr Regul* 1991; **25**: 225–230.
59 Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress, induced anhedonia and its reversal by imipramine. *Psychopharmacol Berl* 1994; **115**: 441–446.
60 Steketee JD, Kalivas PW. Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. *J Pharmacol Exp Ther* 1991; **259**: 916–924.
61 Fontenot MB, Kaplan JR, Manuck SB, Arango V, Mann JJ. Long-term effects of chronic social stress on serotonergic indices in the prefrontal cortex of adult male cynomolgus macaques. *Brain Res* 1995; **705**: 105–108.
62 Kelland MD, Chiodo LA. Serotonergic modulation of midbrain

dopamine systems. In: Ashby CA Jr (ed). *The Modulation of Dopaminergic Neurotransmission by Other Neurotransmitters*. CRC Press: Boca Raton, 1996, pp 87–122.
63 Shively CA, Grant KA, Ehrenkaufer RL, Mach RH, Nader MA. Social stress, depression, and brain dopamine in female cynomolgus monkeys. *Ann NY Acad Sci* 1997; **15**: 574–577.
64 Feenstra MG, Kalsbeek A, Van-Galen H. Neonatal lesions of the ventral tegmental area affect monoaminergic responses to stress in the medial prefrontal cortex and other dopamine projection areas in adulthood. *Brain Res* 1992; **596**: 169–182.
65 Cabib S, Puglisi-Allegra S, D'Amato FR. Effects of postnatal stress on dopamine mesolimbic system responses to aversive experiences in adult life. *Brain Res* 1993; **604**: 232–239.
66 Lipska BK, Chrapusta SJ, Egan MF, Weinberger DR. Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild repeated stress and to chronic haloperidol. *Synapse* 1995; **20**: 125–130.
67 Inglefield JR, Kellogg CK. Hypothalamic GABAA receptor blockade modulates cerebral cortical systems sensitive to acute stressors. *Psychopharmacol Berl* 1994; **116**: 339–345.
68 Biggio G, Concas A, Corda MG, Giorgi O, Sanna E, Serra M GABAergic and dopaminergic transmission in the rat cerebral cortex: effect of stress, anxiolytic and anxiogenic drugs. *Pharmacol Ther* 1990; **48**: 121–142.
69 Boireau A, Dubedat P, Laduron PM, Doble A, Blanchard JC. Preferential decrease in dopamine utilization in prefrontal cortex by zopiclone, diazepam and zolpidem in unstressed rats. *J Pharm Pharmacol* 1990; **42**: 562–565.
70 Kaneyuki H, Yokoo H, Tsuda A, Yoshida M, Mizuki Y, Yamada M *et al*. Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: reversal by diazepam. *Brain Res* 1991; **557**: 154–161.
71 Grobin AC, Roth RH, Deutch AY. Regulation of the prefrontal cortical dopamine system by the neuroactive steroid 3a,21-dihydroxy-5a-pregnane-20-one. *Brain Res* 1992; **578**: 351–356.
72 Hegarty AA, Vogel WH. Modulation of the stress response by ethanol in the rat frontal cortex. *Pharmacol Biochem Behav* 1993; **45**: 327–334.
73 Dazzi L, Motzo C, Imperato A, Serra M, Gessa GL, Biggio G. Modulation of basal and stress-induced release of acetylcholine and dopamine in rat brain by abecarnil and imidazenil, two anxioselective gamma-aminobutyric acidA receptor modulators. *J Pharmacol Exp Ther* 1995; **273**: 241–247.
74 Wedzony K, Mackowiak M, Fijal K, Golembiowska K. Evidence that conditioned stress enhances outflow of dopamine in rat prefrontal cortex: a search for the influence of diazepam and 5-HT1A agonists. *Synapse* 1996; **24**: 240–247.
75 Finlay JM, Zigmond MJ. The effect of stress on central dopaminergic neurons: possible clinical implications. *Neurochem Res* 1997; **22**: 1387–1394.
76 Morrow BA, Clark WA, Roth RH. Stress activation of mesocorticolimbic dopamine neurons: effects of a glycine/NMDA receptor antagonist. *Eur J Pharmacol* 1993; **238**: 255–262.
77 Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. The NMDA glycine site antagonist (+)-HA-966 selectively regulates conditioned stress-induced metabolic activation of the mesoprefrontal cortical dopamine but not serotonin systems: a behavioral, neuroendocrine, and neurochemical study in the rat. *J Neurosci* 1994; **14**: 4937–4950.
78 Keefe KA, Sved AF, Zigmond MJ, Abercrombie ED. Stress-induced dopamine release in the neostriatum: evaluation of the role of action potentials in nigrostriatal dopamine neurons or local initiation by endogenous excitatory amino acids. *J Neurochem* 1993; **61**: 1943–1952.
79 Jedema HP, Moghaddam B. Glutamatergic control of dopamine release during stress in the rat prefrontal cortex. *J Neurochem* 1994; **63**: 785–788.
80 Doherty MD, Gratton A. NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. *Synapse* 1997; **26**: 225–234.
81 Jaskiw GE, Karoum FK, Weinberger DR. Persistent elevations in dopamine and its metabolites in the nucleus accumbens after mild subchronic stress in rats with ibotenic acid lesions of the medial prefrontal cortex. *Brain Res* 1990; **534**: 321–323.
82 Hutson PH, Barton CL. L-701,324, a glycine/NMDA receptor antagonist, blocks the increase of cortical dopamine metabolism by stress and DMCM. *Eur J Pharmacol* 1997; **326**: 127–132.
83 Piazza PV, Le Moal MI. The role of stress in drug self-administration. *TIPS* 1998; **19**: 67–74.
84 De-Kloet ER, Rots NY, Cools AR. Brain-corticosteroid hormone dialogue: slow and persistent. *Cell Mol Neurobiol* 1996; **16**: 345–356.
85 Henry C, Guegant G, Cador M, Arnauld E, Arsaut J, Le Moal M *et al*. Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. *Brain Res* 1995; **685**: 179–186.
86 Alonso SJ, Navarro E, Rodriguez M. Permanent dopaminergic alterations in the n. accumbens after prenatal stress. *Pharmacol Biochem Behav* 1994; **49**: 353–358.
87 Piazza PV, Le Moal ML. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol* 1996; **36**: 359–378.
88 Steketee JD, Kalivas PW. Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. *J Pharmacol Exp Ther* 1991; **259**: 916–924.
89 Rouge Pont F, Marinelli M, Le Moal M, Simon H, Piazza PV. Stress, induced sensitization and glucocorticoids. II. Sensitization of the increase in extracellular dopamine induced by cocaine depends on stress, induced corticosterone secretion. *J Neurosci* 1995; **15**: 7189–7995.
90 Prasad BM, Sorg BA, Ulibarri C, Kalivas PW. Sensitization to stress and psychostimulants. Involvement of dopamine transmission versus the HPA axis. *Ann NY Acad Sci* 1995; **771**: 617–625.
91 Deroche V, Marinelli M, Maccari S, Le Moal M, Simon H, Piazza PV. Stress-induced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. *J Neurosci* 1995; **15**: 7181–7188.
92 Sorg BA, Kalivas PW. Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. *Brain Res* 1991; **559**: 29–36.
93 Sorg BA, Kalivas PW. Effects of cocaine and footshock stress on extracellular dopamine levels in the medial prefrontal cortex. *Neuroscience* 1993; **53**: 695–703.
94 Hamamura T, Fibiger HC. Enhanced stress-induced dopamine release in the prefrontal cortex of amphetamine-sensitized rats. *Eur J Pharmacol* 1993; **237**: 65–71.
95 Diaz Otanez CS, Capriles NR, Cancela LM. D1 and D2 dopamine and opiate receptors are involved in the restraint stress-induced sensitization to the psychostimulant effects of amphetamine. *Pharmacol Biochem Behav* 1997; **58**: 9–14.
96 Hegarty AA, Vogel WH. Modulation of the stress response by ethanol in the rat frontal cortex. *Pharmacol Biochem Behav* 1993; **45**: 327–334.
97 Matsuguchi N, Ida Y, Shirao I, Tsujimaru S. Blocking effects of ethanol on stress, induced activation of rat mesoprefrontal dopamine neurons. *Pharmacol Biochem Behav* 1994; **48**: 297–299.
98 Koechling UM, Amit Z. Effects of CA antagonists on ethanol-induced excitation in habituated and nonhabituated mice: interaction with stress factors? *Pharmacol Biochem Behav* 1993; **44**: 791–796.
99 Berman SM, Noble EP. The D2 dopamine receptor (DRD2) gene and family stress; interactive effects on cognitive functions in children. *Behav Genet* 1997; **27**: 33–43.