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REVIEW

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Stress, depression and the mesolimbic dopamine system

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Abstract The present review was aimed at re-evaluating results obtained from animal models of depression based on experimental stressors in the light of the most recent data on the effects of stress on mesolimbic dopamine (DA) functioning. The data reviewed reveal that the effects of stressful experiences on behaviour and on meso-accumbens DA functioning can be very different or even opposite depending on the behavioural controllability of the situation, the genetic background of the organism and its life history. Exposure to a single unavoidable/uncontrollable aversive experience leads to inhibition of DA release in the accumbens as well as to impaired responding to rewarding and aversive stimuli. Moreover, the data reviewed indicate a strong relationship between these neurochemical and behavioural effects and suggest that they could model stress-induced expression and exacerbation of some depressive symptoms such as anhedonia and feeling of helplessness caused by life events as well as syndromal depression provoked by traumatic experiences in humans. Repeated and chronic stressful experiences can reduce the ability of stressors to disrupt behaviour, induce behavioural sensitisation to psychostimulants and promote adaptive changes of mesolimbic DA functioning. Opposite neural and behavioural changes, however, can be promoted in specific environmental conditions (repeated variable stressful experiences) or in genetically predisposed individuals. Thus, depressive symptoms may not represent the necessary outcome of stress experiences but be promoted by specific environmental conditions and by a genetically determined susceptibility.

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Introduction

The contribution of stress in the induction or exacerbation of depression has been increasingly emphasised in recent years (Anisman and Zacharko 1989, 1990; Willner 1991; Kendler et al. 1995). Moreover, animal studies have demonstrated that either single (acute) exposure to severe stressful experiences or repeated exposures to variable mild stressors impair subsequent learning of active avoidance (learned helplessness) (Weiss et al. 1981; Anisman and Zacharko 1990; Murua et al. 1991), inhibit escape attempts (Garcia-Marquez and Armario 1987; Cancela et al. 1991; Zacharko and Anisman 1991), reduce consumption of palatable foods (Griffiths et al. 1992) or liquids (Katz 1982; Willner et al. 1987) and disrupt responding for intracranial self stimulation (ICSS) (Zacharko et al. 1983; Moreau et al. 1992). These results indicate that, in animal models, stressful experiences promote helplessness and reduced responding for rewards (anhedonia), two major symptoms of depressive states in humans.

Preclinical studies in laboratory animals have also revealed that stressors induce neurochemical and hormonal alterations which are reminiscent of those observed in depressed patients (Katz 1981; Anisman and Zacharko 1990; Willner 1991) and that clinically effective anti-depressant drugs prevent the behavioural alterations promoted by stressful experiences (Weiss et al. 1981; Garcia-Marquez and Armario 1987; Anisman and Zacharko 1990; Cancela et al. 1991; Murua et al. 1991; Zacharko and Anisman 1991; Moreau et al. 1992).

Thus, animal models of depression based on experimental stressors offer a unique opportunity to study alterations of brain functioning induced by stress, a widely recognised psychopathogenic factor in relation to behav-

ioural responses which are analogous with human symptoms.

Several lines of evidence indicate that the behavioural effects elicited by stress could be independently controlled by different brain mechanisms. Thus, inbred strains of mice or rats can show different sensitivity to stress depending on the behavioural response under study, and different types of clinically active antidepressants can be effective in some models and totally ineffective in others (Zacharko and Anisman 1991). These results are in line with the clinically based observation of considerable variability in the symptom profile attending depression and with the hypothesis of a biochemical heterogeneous disorder (Zacharko and Anisman 1991).

Nevertheless, evidence from preclinical investigations implies disturbances of mesolimbic dopamine (DA) function in the pathophysiology of depression (Willner 1983; Swerdlow and Koob 1987; Zacharko and Anisman 1991). Moreover, the mesolimbic DA system appears to be highly susceptible to stress (Cabib et al. 1988; Abercrombie et al. 1989; Puglisi-Allegra and Cabib 1990; Imperato et al. 1991; Sorg and Kalivas 1991; Rougé-Pont et al. 1993). Finally, mesolimbic DA transmission appears to play a major role in defensive responses toward aversive stimuli (Puglisi-Allegra et al. 1989, 1990; Cabib et al. 1990, 1995; Puglisi-Allegra and Cabib 1990) as well as in responses to rewarding stimuli (Wise 1980; Robinson and Berridge 1993; Mas et al. 1995; Berridge 1996).

The last decade has seen an increasing amount of research devoted to the investigation of the effects of stress on mesolimbic DA functioning due to the development of new methodological approaches. These studies have demonstrated that stress promotes profound and complex alterations involving DA release, metabolism and receptors densities in the mesolimbic system. In the following pages we will review the results obtained from such studies in relation with stress-induced behavioural alterations suggested to model depressive symptoms.

Response of the mesolimbic dopamine system to stressful events

For at least one of the animal models of depression, stress-induced impairment of ICSS, there are clear indications of selective involvement of specific DAergic systems. Indeed it was shown that stress experiences reduce the rewarding value of stimulation from the mesocorticolimbic system at both the point of origin of this pathway and terminal areas (Zacharko and Anisman 1991). Instead, stressors do not affect self stimulation from the nigrostriatal pathway (Zacharko et al. 1983). These data clearly point to stress effects that selectively involve the mesocorticolimbic whilst sparing the nigrostriatal system.

It is interesting to note that there is a general consensus in the literature about the ability of mesocortical DA system to respond to almost all stressful experiences. Moreover, it has been recently shown that anxiogenic drugs activate mesocortical DA transmission selectively (Bassareo et al. 1996; but see also contrasting results by McCullog and Salamone 1992). However, there is considerably less agreement as to whether stressful stimuli influence DA activity in other brain regions, including mesolimbic DA activity (Deutch et al. 1985, 1990; Mantz et al. 1989).

In a recent paper it was shown that shock-induced DA outflow in the nucleus accumbens septi (NAS) is dependent on current levels since a significant effect was not observed at current levels below 0.55 mA (Sorg and Kalivas 1991). In line with this observation, studies reporting selective activation of mesocortical DA system utilise 0.20 mA as the current level (Deutch et al. 1985, 1990) whilst a striatal responses was observed at current levels equal to or higher than 1 mA (Abercrombie et al. 1989). Moreover, different or even opposite regional specificity of DA response has been observed using 10 s, or 5 and 8 min of tail pinch. In the first case selective activation of ventral tegmental area (VTA) DA neurones projecting to the frontal cortex (FC) was reported (Mantz et al. 1989), whilst following 5 min of pinching, increased DA release (as measured by intracerebral dialysis) was observed in the striatum (Wheeler et al. 1995). Finally, increased DA release in the NAS but not in the FC (as measured by in vivo voltametry) has been reported following 8 min of tail pinch (D'Angio et al. 1987).

These results suggest regional selectivity of DA response to stress is likely to depend on the severity of the aversive experience. Thus, for shock, the severity of the stressful experience may be related, at least in part, to current levels; instead, for tail pinch it may depend on the duration of the experience. In line with this hypothesis, whilst restraint stress enhances DA outflow in the FC and in the NAS but not in the caudate putamen (CP) (Imperato et al. 1991), rats restrained in a cold environment show altered DA metabolism also in the CP (Dunn and File 1983).

Moreover, regional differences in the extent of the DA response induced by stress have been observed using intracerebral dialysis. Thus, 15 min of tail shock produced nearly a 100% increase of DA outflow in the FC, a 40% increase in the NAS and 25% increase in the striatum (Abercrombie et al. 1989), the effects of tail shock on striatal DA outflow being delayed and transient. Restraint stress, which does not affect DA outflow from striatum, produces an 80% increase of DA outflow in the FC but a 45% increase in the NAS (Imperato et al. 1991). The possibility that these results are due to regional differences in DA turnover cannot be ruled out. Nevertheless, it is also possible that they indicate differential sensitivity of the different brain DA systems to the aversive experiences.

Finally, the parallel regional susceptibility to stress-induced impairment of ICSS and DA response to stress strongly suggests a relationship between these two effects.

Activation and inhibition

Stress has been defined as an organism's response involving generalised activation, promoted by any stimulus that has properties of novelty, threat, conflict or homeostatic imbalance (Ursin 1978). This definition of stress has led most researchers to look for a stress-induced increase in DA release in the mesolimbic DA system. In fact, an increase in DA release in this brain area is the typical effects of psychostimulant drugs which classically promote behavioural activation.

However, several types of stressors promote behavioural inhibition (Cabib 1993 for review). Moreover, enhanced DA transmission in the mesolimbic system appears to promote motivated behaviour and to favour responding to obtain natural as well as pharmacological reinforcers (Wise 1980; Ljunberg et al. 1992; Florino et al. 1993; Robinson and Berridge 1993; Di Chiara 1995; Mas et al. 1995; Berridge 1996). Instead, as previously discussed, long-term ICSS performance deficits have been observed following stressful experiences, suggesting a reduction of motivation or of the reinforcing properties of an otherwise rewarding stimulus in stressed animals (Zacharko et al. 1983; Zacharko and Anisman 1991; Florino et al. 1993).

Stressors can induce different and even opposite behavioural effects depending on the duration of stress experiences. Thus, 30 s of tail pinch was reported to increase ICSS from the medial forebrain bundle (Katz and Roth 1979), while disruption of ICSS from the medial forebrain bundle, VTA and NAS was observed following 60 min of footshock (Zacharko et al. 1983). Moreover, a 20- to 30-min exposure to intermittent footshock was shown to produce an opioid form of analgesia whilst a 3-min exposure to continuous footshock resulted in a non-opioid form (Maier et al. 1983). Finally, brief exposure to a mild stressor (noise) has been shown to increase rats' exploration of an open field (Katz et al. 1981) whilst prolonged exposure to footshock is known to depress locomotor activity. Thus, stressful experiences have different, time-dependent effects and behavioural activation is observable following brief exposure to stressors, whilst prolonged exposure leads to behavioural and motivational impairment (Table 1).

As for mesolimbic DA, several in-vivo and ex-vivo studies report enhanced DA release in the NAS, its major projecting area, in response to stressful experiences (Abercrombie et al. 1989; Puglisi-Allegra and Cabib 1990; Imperato et al. 1991; Sorg and Kalivas 1991; Rougé-Pont et al. 1993). However, in mice subjected to 60 or 120 min of restraint a decrease rather than an increase of DA release was observed in the NAS (Cabib et al. 1988) and restraint-induced enhanced DA outflow in rats appeared to be a temporary response (Imperato et al. 1991). In specifically designed experiments it was demonstrated that exposure to stressors produces a time-dependent biphasic alteration of DA release in the NAS: an initial increase of DA release is followed by a decrease below control levels (Puglisi-Allegra et al. 1991). This effect was evident in two species, rat and mouse, under different stressful conditions, and using different methodological approaches (Puglisi-Allegra et al. 1991). Finally, the time-course of mesoaccumbens DA response was not due to exhaustion of DA synthesis or depletion of DA pools since restrained rats were able to respond with a new increase of DA outflow to the release from the restraining apparatus (Imperato et al. 1991, 1992; Puglisi-Allegra et al. 1991).

Taken together, these results indicate parallel time-courses for behavioural as well as mesoaccumbens DA responses in stressful situations. Indeed, short exposure to stressors enhances mesolimbic DA release, promotes behavioural activation and facilitates reinforced responding, whilst prolonged exposure leads to inhibition of either the behavioural or the neurochemical responses. Moreover, they suggest that stress-induced behavioural alterations used to model depressive symptoms in laboratory conditions are related to the inhibitory phase of mesolimbic DA response to stress (Table 1).

Controllable and uncontrollable stressors

Most of the stress-based experimental models of depression focus on behavioural impairments which are promoted by unavoidable/uncontrollable stressful experiences. Indeed, in specifically designed experiments, it was demonstrated that the behavioural impairing effects of stress are absent in avoidable/controllable aversive situations (Weiss et al. 1981; Maier et al. 1983; Zacharko and Anisman 1991). The basic technique used by these studies is the shocked-yoked situation in which pairs of animals are subjected to a series of electric shocks with only one animal being able to interrupt shock delivery for both by mean of various behavioural responses. In this way the two subjects receive the same amount of shock but experience it either in a "coping" or in a "non-coping" situation.

Using this technique it was demonstrated that mice exposed to a series of foot shocks show an increase of DA release in the NAS if they were allowed to control shock duration (shocked condition) and a decrease of DA release if they were not allowed to exert any control (yoked condition) (Cabib and Puglisi-Allegra 1994). Moreover, it was observed that exposure to the experimental apparatus without shock delivery (sham condition) (Fig. 1) for a time matching the shock procedure (60 min) revealed a mesolimbic DA response only quantitatively different from the response of mice in the yoked group but qualitatively different from the response of mice in the shocked group (Cabib and Puglisi-Allegra 1994).

The latter observation is in line with a number of results which indicate that confinement in an unknown environment is an aversive experience for mice (Misslin et al. 1982; Prince and Anisman 1990; Cabib et al. 1990) and promotes the biphasic DA response by the mesoaccumbens system (Cabib and Puglisi-Allegra 1994) (Fig. 1). Thus, these results indicate that controllable and uncontrollable aversive experiences elicit opposite re-

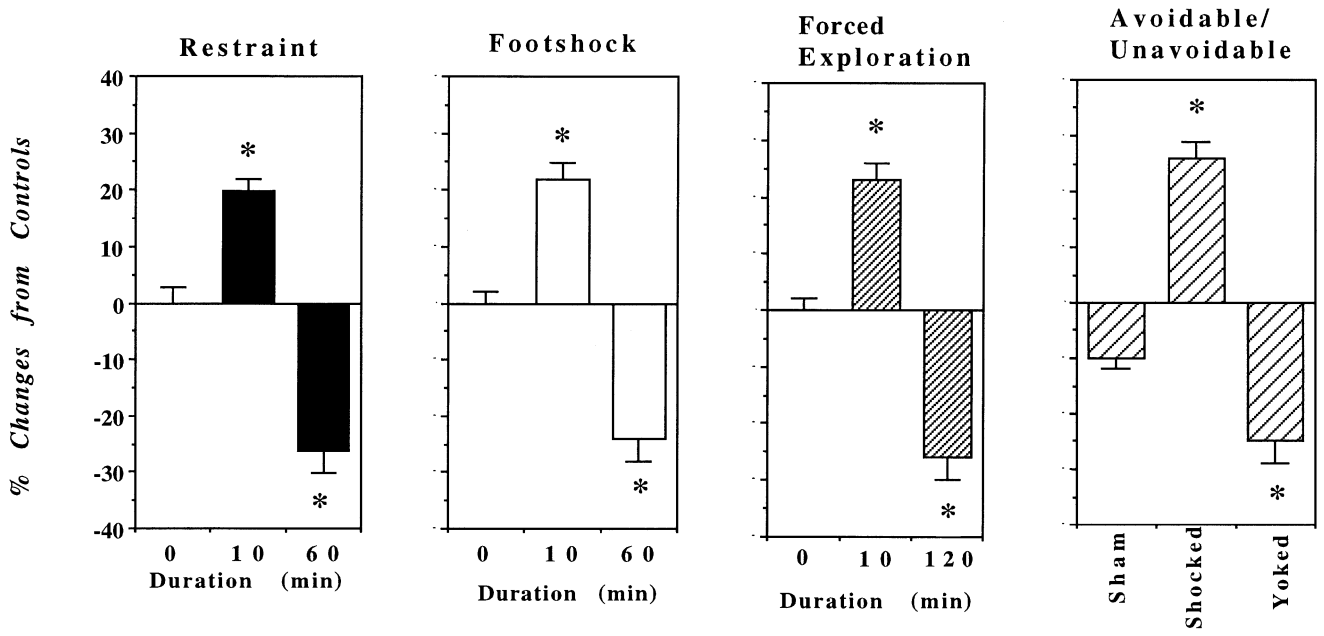

Fig. 1 Time-dependent effects of different stressors (restraint, footshock and forced exploration of a novel environment) or of controllable (Shocked), uncontrollable (Yoked) footshock and exposure to the shock apparatus without shock delivery for 60 min (Sham) on dopamine release in the mouse nucleus accumbens. Results are expressed as % changes in 3-methoxythyramine levels in comparison with controls (unhandled) mice. $*P < 0.05$ in comparison with controls

sponses by the mesolimbic DA system. Moreover, they suggest that in environmental conditions which allow behavioural control, enhanced mesoaccumbens DA release is maintained regardless of severity and duration of the aversive experience.

These results also indicate that the mesolimbic DA response to aversive experiences depends upon the interaction between the organism and the environment. Thus, enhanced mesolimbic DA release is observable when the organism is exposed to a novel, threatening experience. This response is maintained in aversive conditions that allow the organism to control or avoid the aversive stimuli by mean of behavioural responses. Instead, if the situation does not offer opportunities for such behavioural responses, i.e. it is unavoidable and uncontrollable, the initial increase in mesoaccumbens DA release changes into profound inhibition.

Finally, the fact that only unavoidable/uncontrollable stress promotes those behavioural alterations considered to model depressive state supports the existence of a strict relationship between these behavioural responses and stress-induced inhibition of mesolimbic DA release.

Stress, mesolimbic dopamine, motivation and "despair"

The previously discussed data also offer an interpretation of the relationship between behavioural and central effects of stress. Indeed, the biphasic DA response observed during exposure to aversive situations in the NAS can be explained in terms of the meaning that aversive conditions have for the organism. As the organism faces novel aversive events it will first attempt to cope behaviourally with such a pressure. The NAS is a brain structure considered to be involved in activation that increases probability and vigour of responses as well as in motor processes (Le Moal and Simon 1991), therefore activation of the mesoaccumbens DA system is required by the initial, defensive reaction to an aversive condition.

If attempts at behavioural coping meet success, enhanced mesolimbic DA release lasts as long as the aversive experience is maintained. Thus, enhanced mesoaccumbens DA release in stressful conditions is hypothetically related to defensive responses toward the aversive stimulus. A number of experimental observations support this view. Indeed, it has been demonstrated that species-specific defensive responses toward aggressive conspecific are dependent on dopamine transmission (Puglisi-Allegra et al. 1989), that mesoaccumbens DA release is enhanced in animals attacked by conspecifics (Louilot et al. 1986; Puglisi-Allegra and Cabib 1990), and that both mesolimbic DA response and behavioural defence can be elicited by environmental cues previously paired with the aversive experience (Puglisi-Allegra et al. 1989; Puglisi-Allegra and Cabib 1990).

Instead, if, despite the efforts made by the organism, no behavioural coping is possible, a different emotional response takes place which leads to inhibition of both mesolimbic DA release and behavioural responses. Thus, inhibition of mesoaccumbens DA release is related to "coping failure" and subsequent cessation of defensive attempts against the unavoidable/uncontrollable aversive stimulus. A typical example of such conditions is the forced swimming or Porsolt's test. In this test, animals are introduced in a water tank devoid of exits. The initial

behavioural reaction exhibited by the animals, lasting a few minutes, is vigorous attempts at escaping the situation (swimming and struggling to climb the walls of the water tank). However, these active responses are soon abandoned and the animal starts to float in a state of rigid immobility that Porsolt defined as "despair" state and that is reduced by previous chronic but not acute treatment with antidepressants (Porsolt et al. 1978).

Although this test is widely used to screen antidepressant properties of various classes of drugs, it has been criticised as a behavioural model of depressive states. Indeed, several authors have pointed out that immobility in these conditions can be considered an effective defensive response that protects the animals against unnecessary loss of energy and the risk of drowning. Indeed, immobility is a defensive strategy that animals adopt in various kinds of dangerous situations. In aggressive encounters, defeated animals can "freeze" for seconds to minutes and "crouch" in response to social exploration by the opponent (Puglisi-Allegra et al. 1989). However, freezing and crouching in aggressive interactions are accompanied by the same enhanced mesoaccumbens DA release that is observable during active escape attempts (Louilot et al. 1986; Puglisi-Allegra and Cabib 1990). Instead, it has been reported that in the forced swimming test, rats exhibit a dramatic reduction of DA outflow from the ventral striatum within 10 min of permanence in the water tank, that can be reduced by a chronic pretreatment with antidepressants (Rossetti et al. 1993). Moreover, it has been recently shown that antidepressant pretreatment reduces the time spent immobile during the forced swimming test by promoting behavioural adaptive/effective escape responses (Cabib et al. 1995).

As already pointed out, DA transmission in the mesolimbic system appears necessary to the promotion and maintenance of behaviour and for responding to obtain natural as well as pharmacological reinforcers (Wise 1980; Ljunberg et al. 1992; Florino et al. 1993; Robinson and Berridge 1993; Di Chiara 1995; Mas et al. 1995; Berridge 1996). Moreover, increased DA transmission in the ventral striatum has been reported in response to pleasant natural stimuli such as food or a mate (Radhakishun et al. 1988; Meisel et al. 1993). The relationship between mesoaccumbens DA and reinforced responding could thus explain the maintenance of the increase in DA release in escapable/controllable conditions. In these conditions, the activation of mesolimbic DA system could be sustained by the experience of successful coping as well as by the environmental cues which guide the successful response.

In the same way, in unavoidable/uncontrollable stressful situations, inhibition of the behavioural responses as well as of the brain system which sustain them could promote a state of motivational blunting. As already discussed, unavoidable stress promotes deficits in responding for ICSS from the mesoaccumbens. These deficits are relatively long-lasting, being still evident up to 48 h after stress exposure (Zacharko et al. 1983). However, the long-term ICSS performance deficits are only evident in animals that have been tested immediately after inescapable shock and then retested at subsequent intervals (Zacharko and Anisman 1991). This observation has led some authors to suggest that the deficit in responding for brain stimulation could depend on pairing of the transient neurochemical changes associated with the stressor with brain stimulation (Zacharko and Anisman 1991).

In conclusion, behavioural and neurochemical data support the view that a novel aversive experience promotes a multiphasic response whose evolution depends on the interaction between the organism and the environment. Moreover, they indicate that failure to cope with aversive stimuli, by means of species-specific or newly acquired defensive strategies, promotes a specific syndrome, characterised by helplessness and motivational blunting, that is related to reduced mesoaccumbens DA release.

Individual differences, stress and pathology

The data reviewed indicate that stress-induced inhibition of mesoaccumbens DA release could explain both impaired defensive reactions in aversive conditions and deficits in responding for rewarded stimuli observed following stressful experiences. These behavioural impairments are commonly used to model feelings of "helplessness" and anhedonia observed in depressed patients; however, this does not imply that depression is simply due to reduced DA release.

As already observed, depression appears to be a biochemically heterogeneous disease characterised by variability in the symptoms profile (Zacharko and Anisman 1991). Likewise, in animals, there are variations in the behavioural and biochemical alterations provoked by stressful experiences (Zacharko and Anisman 1991). These variations are especially evident when comparing stress responses and their susceptibility to anti-depressant treatments in different strains of mice (Zacharko and Anisman 1991). However, these data do not indicate differences in vulnerability to the impact of stressors, but differences in the profile of stress-induced behavioural disturbances possibly due to the effects of stress on different neurotransmitters or in different brain areas. Strain-specific susceptibility to these effects could thus explain differences in vulnerability to the various behavioural deficits promoted by stress experiences.

Instead, the strict relationship between inhibition of mesoaccumbens DA release and impaired behavioural responding to rewarding and aversive stimuli in animals exposed to a single stressful experience can explain the ability of life events to promote the expression and exacerbation of depressive symptoms such as anhedonia or feelings of helplessness. Moreover, this model can explain how "traumatic" life events promote syndromal depression in individuals with no detectable prior vulnerability (Fowels 1992).

On the other hand, the same depressive symptoms might develop from more subtle negative changes in ev-

Table 1 Summary of the effects of single (acute) stressful experiences

Type of experience	Behaviour		References	Mesoaccumbens DA release	References
Short lasting	Exploration	(+)	Katz et al. (1981)	(+)	Abercrombie et al. (1989)
	IICSS	(+)	Katz and Roth (1979)	(+)	Imperato et al. (1991)
	medial forebrain bundle)			(+)	Puglisi-Allegra and Cabib (1990)
				(+)	Puglisi-Allegra et al. (1991)
	Opioid analgesia	(=)	Maier et al. (1983)	(+)	Rougé-Pont et al. (1993)
				(+)	Sorg and Kalivas (1991)
Long lasting controllable	Active avoidance	(=)	Weiss et al. (1981)	(+)	Cabib and Puglisi-Allegra (1994)
	IICSS (medial forebrain bundle, VTA, NAS)	(=)	Zacharko et al. (1983)		
Long lasting unavoidable	Exploration	(–)	Zacharko and Anisman (1991)	(–)	Cabib and Puglisi-Allegra (1994)
	escape	(–)	Zacharko and Anisman (1991)	(–)	Imperato et al. (1993)
		(–)	Puglisi-Allegra et al. (1990)	(–)	Puglisi-Allegra et al. (1991)
	Active avoidance	(–)	Zacharko and Anisman (1991)	(–)	Rossetti et al. (1993)
		(–)	Weiss et al. (1981)		
	ICSS (medial forebrain bundle, VTA, NAS)	(–)	Zacharko and Anisman (1991)		
	Opioid analgesia	(+)	Maier et al. (1983)		

(+) Enhanced, (–) reduced, (=) no changes

eryday life (Willner 1991). Animal models of such conditions look for the effects of repeated exposure to mild and variable aversive events rather than to the effects of a single, severe stress experience. Impaired responding for rewarding or aversive stimuli as well as alteration of mesolimbic DA functioning have been also observed in these conditions(Garcia-Marquez and Armario 1987; Willner et al. 1987; Zebrowska-Lupina et al. 1991; Griffiths et al. 1992; Moreau et al. 1992; Murua and Molina 1992). Moreover, there are a few reports of behavioural and neurochemical alterations in animals exposed to chronic unavoidable stressful conditions.

In the following pages we will review results obtained by these studies pointing to the relationship between alteration of mesoaccumbens DA functioning and behavioural deficits.

Repeated and chronic stress, mesolimbic DA functioning and adaptation

Repeated variable stressful experiences

Several independent researches have demonstrated that exposure to repeated and variable aversive experiences promotes deficits in responding for rewarding stimuli as indicated by marked and persistent reduction in the intake of palatable liquids (Willner et al. 1987) and food (Griffiths et al. 1992) or in responding for ICSS from VTA (Moreau et al. 1992). Moreover, deficits in responding to aversive experiences have been also reported following exposure to repeated variable stressors. These deficits involve increased immobility in the forced swimming test (Garcia-Marquez and Armario 1987), reduced footshock-induced fighting (Zebrowska-Lupina et al. 1991) and impaired escape responses (Murua and Molina 1992). These effects were all reversible by chronic treatments with clinically effective antidepressants.

Thus the behavioural profile promoted by repeated variable stress experiences appears very similar to that observed following a single experience with severe stressors. However, it was demonstrated that the different stressors used were not capable of promoting the behavioural deficits by itself (Willner 1991). Moreover, repeated exposure to the same stressor over days was shown to reduce rather than increase the behavioural deficits promoted by severe stressors (Platt and Stone 1982; Puglisi-Allegra et al. 1990; Cancela et al. 1991). Thus the behavioural effects of repeated variable stress appear to depend on the unpredictability of the aversive experiences.

Several lines of evidence point to an involvement of altered mesolimbic DA functioning in the behavioural deficits promoted by repeated variable stressful experiences. Indeed, altered sensitivity of DA autoreceptors is suggested by pharmacological studies (Muscat et al. 1988). Moreover, following repeated variable stressful experiences, rats present increased levels of DA and reduced specific binding to DA D_2 receptors in the limbic forebrain but not in the caudate nucleus or septal area (Willner et al. 1991; Papp et al. 1994). Finally, the repeated variable stress paradigm has been shown to promote hyposensitivity to the behavioural activating effects of amphetamine (Papp et al. 1991) or exposure to a novel environment (Katz et al. 1981).

The final observation suggests that repeated variable stress could result in reduced responses by the mesolimbic DA system to activating stimuli. Indeed, as previously discussed, behavioural activation promoted by psychostimulant and novel aversive experiences is related to enhanced DA release in the mesoaccumbens system. In-

terestingly, repeated exposure to the same stressor has been shown to promote enhanced mesoaccumbens DA response to psychostimulant challenge and this effect has been related to enhanced motor response to the drug (Sorg and Kalivas 1991). It thus seems that repeated exposure to the same stressor and repeated exposure to variable aversive experiences promote opposite behavioural alterations (Table 2) and, possibly, opposite changes in mesolimbic DA functioning.

Adaptation to stress and behavioural sensitisation

As previously observed, some of the behaviourally impairing effects of stress are progressively reduced with repeated exposure to a given stressor (Platt and Stone 1982; Puglisi-Allegra et al. 1990; Cancela et al. 1991; Cabib et al. 1995). This could suggest that the organism is capable to reduce the disruptive effects of stress on behaviour by activating adaptive processes. In line with this hypothesis, exposure to unavoidable stress decreases the climbing behaviour exhibited by mice exposed to a novel environment, an effect that is lost following repeated exposure to restraint (Puglisi-Allegra et al. 1990). Several lines of evidence suggest that climbing behaviour is a defensive-escape response to potentially dangerous situations (Cabib et al. 1990; Puglisi-Allegra et al. 1990). Adaptive processes promoted by repeated stressful experiences could thus enable the organism to reinstate defensive responses in the presence of unavoidable/uncontrollable stressors.

Animals repeatedly exposed to the same stressful experience also show enhanced behavioural response to psychostimulant challenge (Robinson 1988; Sorg and Kalivas 1991; Badiani et al. 1992). Such a phenomenon is normally observed following repeated systemic injections of different types of psychostimulants and is known as "behavioral sensitisation" (Robinson 1988). Stress-induced behavioural sensitisation to psychostimulants is only observable following repeated exposure to unavoidable/uncontrollable aversive experiences, whereas avoidable/controllable aversive experiences are devoid of such effect (MacLennan and Maier 1983). This last observation supports the view that behavioural sensitisation could be the outcome of functional alterations involved in adaptation to repeated or chronic stressful experiences that do not allow behavioural coping.

Repeatedly or chronically stressed rats also show enhanced response to the effects of cocaine on DA release in the NAS (Sorg and Kalivas 1991; Rougé-Pont et al. 1996). Consequently, stress-induced behavioural sensitisation to psychostimulants may depend on enhanced response of the mesolimbic DA system to the stimulating effects of these drugs. This does not mean, however, that adaptation to repeated stressful experiences involves a progressive reduction of the inhibitory effects of stress on mesolimbic DA release (Fig. 2). Indeed, repeated exposures (six consecutive daily experiences) to 60 min of restraint stress promote progressive reduction of stress-induced DA release and parallel anticipation of inhibition of mesolimbic DA release (Imperato et al. 1992, 1993; Cabib and Puglisi-Allegra 1996).

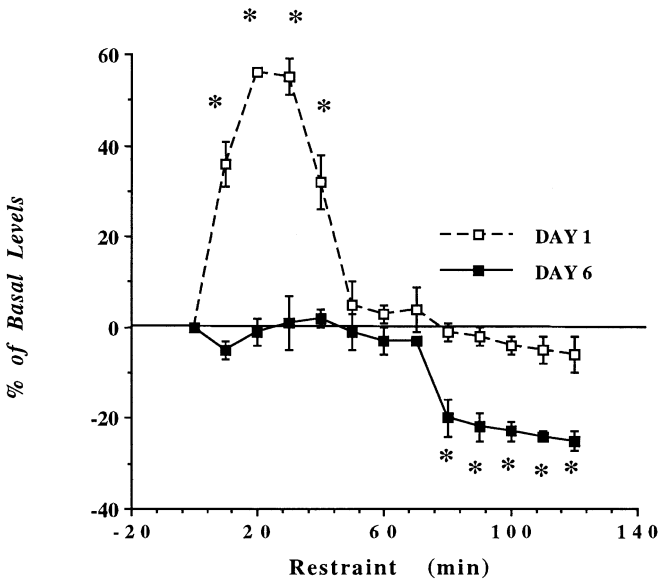

Fig. 2 Effects of 120 min of restraint stress on DA outflow (% changes ± SEM from basal DA levels) from the NAS of naive rats (day 1) or rats repeatedly exposed to the stressor (day 6). $*P < 0.05$ in comparison with basal levels

Instead, adaptation induced by repeated stressful experiences could involve changes in sensitivity of DA receptors (Cabib et al. 1985; Cabib and Puglisi-Allegra 1991) or changes in the interaction among brain systems. Indeed, it has been shown that mesoaccumbens DA activation by mild aversive stimuli is maintained under the inhibitory control of prefrontal cortex (Deutch et al. 1990). Moreover, whilst mesolimbic DA activation is reduced by repeated exposure to the same stressor, the frontocortical DA response is maintained throughout (Cabib and Puglisi-Allegra 1996). Finally, it has been suggested that behavioural sensitisation is accompanied by sensitisation of psychostymulant-induced DA release from the mesoaccumbens and desensitisation of psychostymulant-induced DA release from the mesocortical DA system (Sorg and Kalivas 1991, 1993).

Another limbic area that could be involved is the hippocampus that receives DA imputs from the VTA as the accumbens and prefrontal cortex. Thus, hippocampal lesions were shown to facilitate behavioural activation and mesolimbic DA release promoted by amphetamine (Wilkinson et al. 1993) and prevent behavioural sensitisation promoted by repeated amphetamine (Yoshikawa et al. 1991).

Taken together, these data suggest that adaptive changes at the level of mesolimbic and mesocortical DA systems could allow the organism to reduce some of the disruptive effects of stress on behaviour upon repeated experiences with the stressor. This phenomenon contrasts with the clinical observation that depressive states do not ameliorate but are actually worsened if the stress-

Table 2 Summary of the effects of repeated and chronic stressful experiences

Type of experience	Behaviour		References
Repeated invariable (uncontrollable) or chronic	Exploration	(+)	Puglisi-Allegra et al. (1990)
	Immobility in the forced swimming test	(–)	Cabib et al. (1995)
		(–)	Platt and Stone (1982)
	Behavioural response to psychostimulants	(+)	Badiani et al. (1992)
		(+)	Cabib et al. (1995)
		(+)	MacLennan and Maier (1983)
		(+)	Sorg and Kalivas (1991)
Repeated invariable (controllable)	Behavioural response to psychostimulans	(=)	MacLennan and Maier (1983)
Repeated variable	Exploration	(–)	Katz et al. (1981)
	Immobility in the forced swimming test	(+)	Garcia Marquez and Armario (1987)
	Behavioural response to psychostimulants	(–)	Papp et al. (1991)
	Intake of palatable foods or liquids	(–)	Griffiths et al. (1992)
		(–)	Willner et al. (1987)
	ICSS (VTA)	(–)	Moreau et al. (1992)
	Footshock-induced aggression	(–)	Zebrowska-Lupina et al. (1991)
	Escape	(–)	Murua and Molina (1992)

(+) Enhanced, (–) reduced, (=) no changes

ful conditions are maintained. However, adaptive processes could be the basis of an interaction between genetic and environmental factors which may orient adaptation towards pathological outcomes.

Other forms of adaptation

Several lines of evidence indicate that adaptation to stress is influenced the individual's genetic background. As already discussed, repeated exposure to restraint reduces the inhibitory effect of this stressor on the climbing behaviour exhibited by mice in a novel environment. However, this effect shows marked strain-dependent differences. Tolerance to the inhibitory effect of restraint on climbing behaviour is evident in repeatedly stressed mice of the DBA/2 inbred strain whilst mice of the C57BL/6 strain actually show an increase of stress-induced climbing inhibition (Puglisi-Allegra et al. 1990). Moreover, when exposed to repeated variable stressors, C57BL/6 mice show progressive reduction in consumption of a palatable food whilst the opposite is true for mice of the DBA/2 strain (Griffiths et al. 1992) (Table 3). Finally, a chronic stress regimen, restricted feeding, induces a reduction of immobility in the forced swimming test in mice if the DBA/2 strain (Cabib et al. 1995) and an increase in mice of the C57BL/6 strain (Cabib et al., in preparation) (Fig. 3).

These data suggest that different adaptation to repeated and chronic stressful experiences can be observed in organisms characterised by a different genetic constitution. In line with this hypothesis, repeatedly stressed mice of the C57BL/6 and DBA/2 strains show different alterations in the time-course of the biphasic mesoaccumbens DA response to stress. Indeed, although the activation phase is no more evident in either strains, mice of the DBA/2 strain show a delayed onset of the inhibitory

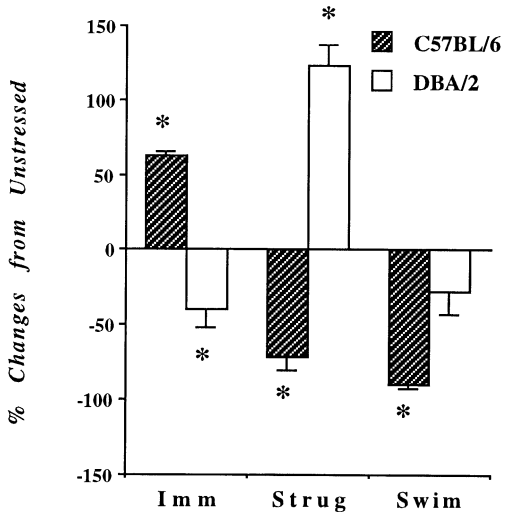

Fig. 3 Behavioural responses in the Porsolt's test presented by food-restricted mice of the C57BL/6 and DBA/2 strain. Results are expressed as % changes from behaviour of unstressed (free fed) mice of the same strain. Testing followed 48 h of free feeding. $^{*}P < 0.05$ in comparison with unstressed mice of the same strain

phase (Cabib and Puglisi-Allegra, in preparation). Moreover, following repeated stressful experiences, DBA/2 mice show reduced sensitivity to the inhibitory effects of low doses of the DA agonist apomorphine on climbing behaviour and mesoaccumbens DA metabolism, indicating hyposensitivity of mesolimbic DA autoreceptors (Cabib and Puglisi-Allegra 1991). By contrast, a marked increase in both the behavioural and the biochemical effects of these same doses of apomorphine were observed in repeatedly stressed C57BL/6 mice, indicating opposite alterations of DA autoreceptors sensitivity (Cabib and Puglisi-Allegra 1991).

Strain-dependent differences are not sufficient to establish the role of genetic factors in the control of pheno-

Table 3 Summary of the effects of repeated and chronic stressful experiences in two inbred strains of mice

Behaviour	C57BL/6	DBA/2	References
Exploration	(–)	(+)	Puglisi-Allegra et al. (1990)
Immobility in the forced swimming test	(+)		Cabib et al., in preparation
		(–)	Cabib et al. (1995)
Behavioural response to psychostimulats	(=)	(+)	Badiani et al. (1992)
Intake of palatable foods	(–)	(+)	Griffiths et al. (1992)
Behavioural response to low doses of apomorphine	(+)	(–)	Cabib and Puglisi-Allegra (1991)

(+) Enhanced, (–) reduced, (=) no changes

types. However, a classic genetic analysis involving the DBA/2 and C57BL/2 parental strain, their F1 and F2 hybrids and backcrosses (F1 X C57; F1 X DBA) as well as an analysis of Quantitative Trait Loci in Recombinant Inbred strains have been conducted on the behavioural response to low doses of apomorphine in stressed mice (Cabib et al. 1985; Oliverio et al. 1992). The results obtained indicated that mesoaccumbens DA autoreceptor sensitivity is a polygenic trait controlled by a major genotype × stress interaction.

Finally, autoradiographic quantification of D_2/D_3 receptors in the VTA revealed a stress-induced decrease of these receptors in mice of the DBA/2 strain and an increase in the C57BL/6 (Puglisi-Allegra et al. 1994). It should be noted that a transient reduction of DA autoreceptors sensitivity in the VTA has been demonstrated following repeated psychostimulant administrations (Ackerman and White 1990; Kalivas and Duffy 1993). Moreover, it has been suggested that this phenomenon could be involved in the development of behavioural sensitisation to psychostimulants (Kalivas and Duffy 1993). Interestingly, repeated restraint promotes the development of behavioural sensitisation to amphetamine only in mice of the DBA/2 strain (Badiani et al. 1992).

Consequently, these data further support the view that stress-induced behavioural sensitisation could represent the side-effects of changes in mesolimbic DA functioning promoted by adaptation to stress. Moreover, they indicate that genotype may regulate adaptation of the mesolimbic DA system to stress leading to opposite alterations and different behavioural changes. This possibility could have great clinical relevance since a role of genotype-dependent susceptibility to depression has been postulated (Fowels 1992; Oliverio et al. 1992; Kendler et al. 1995).

Pharmacological implications

As repeatedly observed, different types of clinically effective antidepressants prevent the behavioural effects of acute stress and allow recovery from those promoted by repeated variable stress. These data appear to suggest that antidepressants could produce adaptive changes in resistant individuals or in environmental conditions which prevent adaptation. However, contrasting results have been obtained on the ability of chronic antidepressant treatments to induce DA autoreceptor hyposensitivity or behavioural sensitisation (Serra et al. 1979, 1990; Chiodo et al. 1980; Willner and Montgomery 1981; Maj et al. 1985; Plaznik et al. 1987; Delini-Stula et al. 1988; Cabib et al. 1995) indicating that the mode of action of therapeutic drugs may not overlap with stress-induced adaptation.

Recent results appear to support this conclusion. These results were obtained using the antidepressant minaprine, since this substance is thought to affect central DA functioning (Imperato et al. 1994). However, the antidepressant is devoid of effects on DA release in ventral striatum as well as on motor responses (Imperato et al. 1994) which, as already discussed, are the typical effects of psychostimulants and stressful events. Consequently, these data indicate that the DAergic profile of minaprine is distinguishable from that of acute psychostimulants or stress.

Antidepressants are known to develop clinical efficacy following repeated administration. Following subchronic treatment, minaprine prevents the inhibitory effects of stress on the climbing response (Cabib et al. 1995), reduces immobility in the forced swimming test (Imperato et al. 1994; Cabib et al. 1995) and promotes DA release in the ventral striatum in a dose-dependent fashion (Imperato et al. 1994). Moreover, either chronic stress or amphetamine pretreatment are as effective as the antidepressant in reducing immobility in the Porsolt's test (Cabib et al. 1995). These results suggest that the clinical efficacy of minaprine could depend on its ability to prevent the disruptive effects of stress on behaviour by promoting alterations of mesolimbic DA functioning similar to those promoted by repeated and chronic stress.

On the other hand, the behavioural responses promoted by the various treatments are markedly different. Thus, chronically stressed animals and animals pretreated with amphetamine show high levels of struggling (vigorous attempts at climbing the glass walls of the tank) in restricted areas of the swimming tank, whilst minaprine-treated animals show mostly swimming (Cabib et al. 1995). Moreover, while a behavioural sensitisation to amphetamine challenge is evident following either chronic stress or amphetamine, no sensitisation is observable in minaprine-treated animals (Cabib et al. 1995). Finally, no signs of altered sensitivity to low doses of apomorphine are observable in minaprine-treated animals (Cabib et al. 1995). These data support the view that clinically effective antidepressants induce adaptive changes that might also involve the mesolimbic DA system, however these changes are clearly different from those promoted by chronic/repeated stressful experiences.

The latter observation has important clinical implications. As repeatedly observed, some of the adaptive changes promoted by chronic or repeated stressful experiences may be responsible for stress-induced behavioural sensitisation. This phenomenon is also produced by repeated psychostimulants administration, an experimental procedure used to model psychotic-like responses in animals (Segal and Schuckit 1983; Robinson 1988; Lyon 1991). Moreover, several lines of evidence suggest that behavioural sensitisation observed in animal studies could share homologies with drug dependence in humans (Robinson and Berridge 1993). Consequently, adaptation to stress may represent a risky chance for the organism since it increases susceptibility to specific behavioral disorders.

Preclinical research on antidepressants should thus acknowledge that some alterations of mesolimbic DA functioning might represent undesirable side effects. Moreover, since adaptation to stress is so costly for the organism, pharmacological intervention aimed at preventing the alterations required by this adaptation could be extremely helpful. This could be attained through substances capable of affecting mesolimbic DA functioning in a way different from the one promoted by stress or through substances which prevent or reduce those central effects of stress responsible of adaptive changes. The study of mesolimbic DA response and adaptation in stressful conditions could be most suitable for such research.

Conclusions

At this point it is possible to draw some important general conclusions. It is indubitably the case that exposure to stressful events provokes major behavioural and neurochemical effects involving mesolimbic DA functioning. However, the type of alterations induced by these experiences can be extremely different, or even opposite in direction depending on the severity of the stressor, the behavioural controllability of the situation, the predictability of the experience, the genetic background of the organism and its life history (previous stress experiences). The variety of alterations and the number of factors implicated predict large individual variability in stress outcomes, thus explaining individual differences in susceptibility, prognosis and relapse for behavioural disorders including depressive states.

Exposure to unavoidable/uncontrollable aversive experiences leads to inhibition of DA release in the mesoaccumbens DA system as well as impaired responding to rewarding and aversive stimuli. The data reviewed indicate a strong relationship between these neurochemical and behavioural responses. Moreover, they suggest that these alterations could model stress-induced expression and exacerbation of some depressive symptoms such as anhedonia and feelings of helplessness by life events as well as syndromal depression provoked by traumatic experiences in humans. On the other hand, other types of depressive symptoms may be unrelated to altered mesoaccumbens DA transmission.

Repeated and chronic stressful experiences can reduce the ability of stressors to disrupt behaviour, induce behavioural sensitisation to psychostimulants and promote adaptive changes of mesolimbic DA functioning. Opposite neural and behavioural changes, however, can be promoted in specific environmental conditions (variable stressful experiences) or in genetically susceptible individuals. Thus, depressive symptoms may not represent the necessary outcome of stress experiences but be promoted by specific environmental conditions and by a genetically determined susceptibility.

However, successful adaptation to stress can be dangerous for the organism since it provokes behavioural sensitisation. The latter phenomenon has been suggested to share neural substrata with psychotic syndromes as well as with susceptibility to drug seeking behaviour. Consequently, preclinical research aimed at developing new pharmacological approaches to depression should search for drugs devoid of behaviourally sensitising effects and capable of protecting the organism against the devastating effects of adaptation to stress. This could be profoundly facilitated by the study of the neural mechanisms that underlie such phenomenon.

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