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Stress: A Major Variable in the Psychopharmacologic Response

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STANFORD, S. C. *Stress: A major variable in the psychopharmacologic response.* PHARMACOL BIOCHEM BEHAV **54**(1) 211–217, 1996.—The role of central monoaminergic neurones in stress is undisputed, albeit undefined. This is partly because little is known about the influence of the type or intensity of stress, or subjects' stress history, on monoaminergic transmission. That the presynaptic response is stimulus specific is underlined by a study using in vivo microdialysis in freely moving rats. This indicated that graded changes in noradrenaline efflux in the frontal cortex are produced by progressively increasing the number of novel features in the rats' environment. The influence of receptor status on behavioural responses to stress also depends on the stress imposed. This was suggested by studies showing that rats' behavioural response to stress correlated with the density of cortical β-adrenoceptors. But the precise relationship again depended on features of the stress, possibly its intensity. Finally, it seems that even a single stress challenge (a 6-min swim) causes a long-latency increase in the density of 5-HT_{2A} receptors in mouse cortex. This upregulation was prevented by a history of intraperitoneal injections of saline but not by injections of the monoamine reuptake blocker sibutramine hydrochloride. Collectively, these experiments emphasize the importance of stress as an experimental variable when studying the actions of psychotropic drugs.

β-Adrenoceptors 5-Hydroxytryptamine 5-Hydroxytryptamine$_{2A}$ Receptors Individual differences Monoamine Noradrenaline Stress Stress resistance

POSSIBLY all neurotransmitters and neuromodulators in the brain participate in the stress response, but particular attention has been devoted to the role of 5-hydroxytryptamine (5-HT) and noradrenaline. This reflects the longstanding link between stress and increased catecholamine release by the sympathoadrenal system in the periphery. There is also evidence that noradrenergic and 5-hydroxytryptaminergic function are abnormal in anxiety and depression, CNS disorders which are provoked or aggravated by stress (9). Such evidence is based largely on preclinical studies of the pharmacology of anxiolytic and antidepressant drugs. However, although preclinical screening of these compounds typically involves scoring their effect on animals' behavioural response to stress, relatively few studies have looked at their impact on the neurochemical response to stress.

This is an important area because strikingly different types of stress are used to study the behavioural effects of these two groups of compounds. In general, preclinical studies of antidepressants use stress involving inescapable foot-shock (5), enforced swimming (25), or immobilization (4). These procedures obviously incorporate prominent somatosensory stimulation, as well as the psychologically aversive features of inescapability and/or uncontrollability. In stark contrast, stress used to monitor the behavioural effects of anxiolytic agents traditionally involves stimuli, such as signals of conflict or frustration, or novelty (18). Such stimuli do not involve somatosensory discomfort and arguably resemble conditions experienced by both rats and humans in their natural environment. These forms of nonnoxious, "naturalistic" stress are thought to be key factors in shaping behaviour (9,17).

Key questions arising from these disparate approaches are how monoaminergic transmission codes the quality or intensity of stress, and how this coding influences behaviour. Evidence discussed below indicates that neurochemical and behavioural changes induced by stress, as well as the effects of psychotropic drugs on these changes, depend on both specific features of concurrent stress and subjects' history.

SPECIFICITY OF THE PRESYNAPTIC RESPONSE TO STRESS

Many different techniques have been developed to estimate changes in the rate of release of noradrenaline and 5-HT. Until recently, these depended on indirect indices of neuronal activity based on neurochemical measurements ex vivo. Routine procedures include evaluation of the rate of transmitter synthesis or elimination, or measurement of the accumulation of the metabolites of noradrenaline and 5-HT. From such studies, it is broadly inferred that stress activates central nor-

adrenergic and 5-hydroxytryptaminergic neurones. However, the extent of this activation varies considerably between different brain regions and animal strains [reviewed in (31)].

For noradrenergic neurones at least, it is also evident that the neurochemical effects of somatosensory stress can be distinguished from those of naturalistic stress. This is because inescapable foot-shock, or forced swimming, commonly depletes transmitter stores in several brain regions (5,43). It is thought that this depletion might be responsible for the changes in behaviour caused by these forms of stress (6,45). In contrast, transmitter stores are rarely depleted after exposure to naturalistic stimuli such as novelty or exposure to conditioned aversive cues [however, see (46)]. Yet, noradrenergic and 5-hydroxytryptaminergic neurones are activated by these types of stress. This is suggested by reports that aversive, naturalistic stimuli increase the firing rate of noradrenergic neurones in the locus coeruleus (8,26). Further evidence comes from studies indicating that naturalistic stress increases both the accumulation of the noradrenaline metabolite MHPG.SO4 in the terminal field (12,41) and the concentration of 5-HT in the extracellular fluid (47).

Collectively, these findings suggest that release of noradrenaline is greater during inescapable foot-shock than during naturalistic stress. In turn, this implies that noradrenergic neurones code their response to different types of stress by varying the amount of transmitter they release. So far, such specificity of the stress response has not been confirmed experimentally.

Recently, in vivo microdialysis has been used to investigate whether the rate of noradrenaline release depends on features of the stress experienced. Using this technique, it has been shown that efflux of noradrenaline in freely moving animals is increased by a wide range of somatosensory [e.g., immobilization (2)] or naturalistic [e.g., conditioned aversive cues (49)] stimuli. However, differences in experimental protocols mean that changes in transmitter efflux in these various studies cannot be compared directly. To resolve this difficulty, a recent series of experiments compared the changes in noradrenaline efflux caused by a cumulative series of naturalistic stimuli.

First, animals were transferred to a novel cage with a light intensity similar to that of the home cage (300 lx). This increased noradrenaline efflux in the frontal cortex compared with that in the prestress (basal) samples. However, the increase was not significantly greater than that caused by the handling required for the transfer (14,33) (Fig. 1B). When the light intensity of the novel cage was increased to 1500 lx, there was a greater increase in noradrenaline efflux. The increase was statistically significant compared with basal efflux (maximum increase 68%) and declined slowly during the 2 h in the novel arena (Fig. 1C). The highest levels of extracellular noradrenaline were found after transfer to the brightly lit cage when this also contained an unfamiliar conspecific. These experimental conditions also produced a prolonged tonic increase in noradrenaline efflux (Fig. 1D). It is unlikely that this sustained response is due to the inadequate elimination of noradrenaline from the extracellular space, because noradrenaline levels in the dialysates diminished rapidly when animals were returned to their home cages.

Despite these pronounced changes in noradrenaline efflux, it should not be assumed that the stimuli used in these studies are all aversive. However, it is relevant that these stimuli mimic conditions (novel arena, high light intensity, and the presence of a conspecific) used in the rat social interaction test. Here they produce changes in behaviour which are prevented by benzodiazepines (16). Consistent with this effect, a

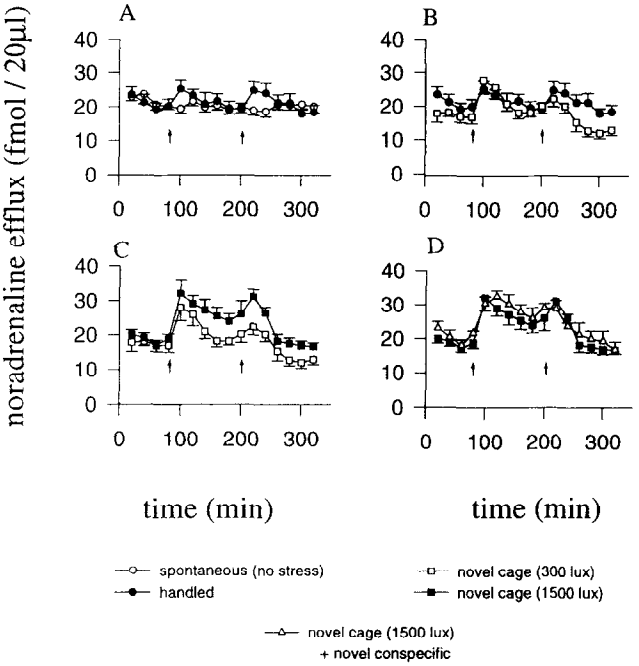

FIG. 1. Changes in the concentration of noradrenaline in dialysates of rat frontal cortex during exposure to aversive naturalistic stimuli. Values show mean ± SEM; sample n 6–12 for each point. Basal efflux was measured in four consecutive samples. Following this, animals were either: left in their home cage throughout (spontaneous); handled while in their home cage, at the times indicated by the arrows (80 and 200 min); or transferred to a novel cage after 80 min and returned to their home cage at 200 min (arrows). Statistical analysis used split-plot ANOVA on bins of three consecutive samples. Noradrenaline efflux in the novel cage (1500 lx) was significantly greater than basal efflux during both the 1st [$F(1, 20) = 12.89$; $p < 0.002$] and the 2nd h [$F(1, 20) = 5.39$; $p = 0.031$]. This increase was not significantly greater than that caused by handling. The presence of an unfamiliar conspecific in the novel cage caused a sustained increase in noradrenaline efflux. This was significantly greater than that caused by handling during the 1st h [$F(1, 10) = 7.54$; $p = 0.021$] and did not decline significantly during the 2nd h in the novel cage [$F(1, 10) = 1.26$; $p = 0.289$].

dose of diazepam, which typically modifies behaviour in this test, attenuated the increase in noradrenaline efflux caused by novelty and bright light (unpublished) (Fig. 2). This finding complements evidence from early studies that benzodiazepines prevent the increase in noradrenaline turnover induced by somatosensory stressors such as foot-shock (40) or immobilization (13).

Collectively, these experiments suggest that subtle changes in animals' environment have marked effects on noradrenaline efflux in the cerebral cortex. The changes in efflux involve both phasic and tonic components of the noradrenergic stress response. This means that both spontaneous efflux and the effects of drugs on changes in efflux could depend on environmental conditions at the time of measurement.

SPECIFICITY OF RECEPTOR STATUS IN THE BEHAVIOURAL RESPONSE TO STRESS

The behavioural response to stress depends on receptor status (density and affinity state) as well as presynaptic mechanisms governing transmitter release. This was highlighted by reports that repeated stress reduces the density of cortical β-

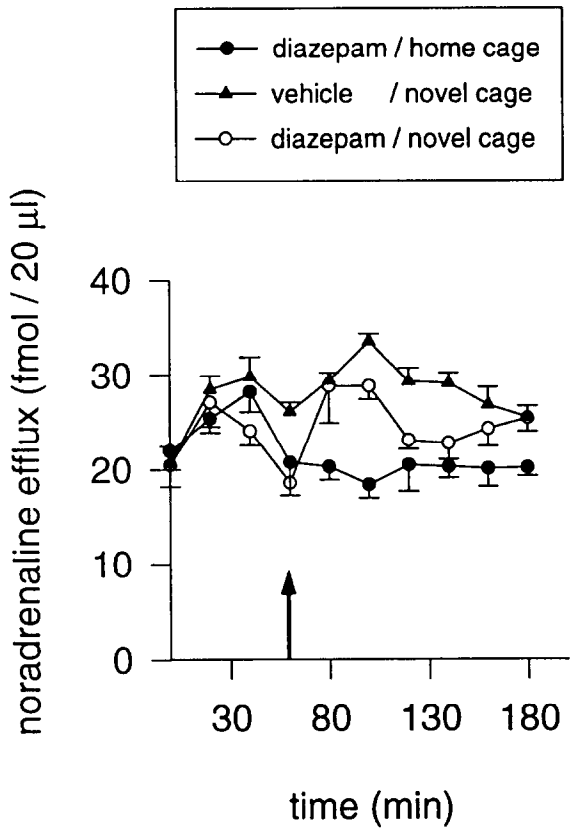

FIG. 2. Effect of diazepam on the increase in noradrenaline efflux in rat frontal cortex caused by transfer to a novel cage (1500 lx) containing an unfamiliar conspecific. Values show mean ± SEM; sample n 5 or 6 for each point. At time 0, animals were injected with either 1% methylcellulose vehicle (2 ml/kg) or diazepam (3 mg/kg, IP) and replaced in their home cage. One hour later (arrow), vehicle-injected rats and a group of diazepam-injected rats were transferred individually to novel cages. A further group of diazepam-injected rats remained in their home cages. While in their home cages, there was no significant difference in noradrenaline efflux in vehicle-injected and diazepam-injected animals [$F(1, 10) = 1.47$; $p = 0.217$]. Compared with vehicle-injected rats, diazepam significantly attenuated noradrenaline efflux during the 1st h in the novel cage [$F(1, 10) = 6.81$; $p = 0.026$].

adrenoceptors in rat cerebral cortex (downregulation) (Table 1) or uncouples the transmitter binding site from its second messenger complex (desensitization) (36). This led to the suggestion that diminished β-adrenoceptor function in the cerebral cortex, including that resulting from receptor downregulation, was an important element of adaptation to stress (37). This is supported to some extent by evidence that physiologic consequences (e.g., gastric ulceration) of a single bout of immobilization are diminished in rats which have experienced repeated restraint (39). A corollary of this theory is that β-adrenoceptor downregulation confers resistance to the effect of an acute stress challenge. If this is the case, then the relationship between stress resistance and reduced β-adrenoceptor activation should hold true for any group of individuals. This leads to the prediction that subjects with the lowest density of cortical β-adrenoceptors will show the greatest resistance to stress. This prediction was tested in a series of experiments which investigated the relationship between the density of cortical β-adrenoceptors and behavioural responses to stress.

One difficulty with studies of this type lies in distinguishing whether differences in the behavioural response to stress indicate adaptation, maladaptation, or, in extreme cases, a failure to respond at all. However, when evaluating the behavioural response to conditioned aversive cues, it is generally agreed that animals which display the least disruption of ongoing behaviour are the most resistant to the stress. Similarly, in the case of novelty, it is inferred that animals which display the least avoidance of the aversive novel features of their environment are those which are most resistant to stress. To some extent, these interpretations of behaviour during stress are dependent on the effects of antianxiety drugs. These drugs consistently prevent the disruption of behaviour induced by naturalistic stress.

Against this background, a series of experiments tested the hypothesis that the impact of stress on behaviour would be least in animals with the lowest density of β-adrenoceptors. The first experiments evaluated the behavioural response and cortical β-adrenoceptor status of individual animals exposed to a novel open field. In this experimental paradigm, the extent of exploratory behaviour directed toward, or within, the centre of the arena is used as an index of resistance to stress (7,10). The density of cortical β-adrenoceptors in individual animals was measured ex vivo immediately after scoring their behaviour for 4 min in the open field. Across the whole group of subjects, there was a statistically significant correlation between receptor density and resistance to stress (Fig. 3A). A similar correlation was found when radial movements were expressed as a proportion of animals' total movement score (Fig. 3B). This indicates that the correlation was independent of animals' overall locomotor activity. However, the relationship was such that animals with the greatest density of β-adrenoceptors were the most stress resistant (27).

A similar relationship indicating that the density of β-adrenoceptors correlates positively with resistance to stress was also found when using a different stress paradigm: frustrative nonreward. In this test, withholding food reward from rats trained to run down a runway constitutes the stress. Extensive evidence indicates that animals that are slowest to extinguish (i.e., those that persist in moving down the runway) are the most resistant to the stress of nonreward (17). Except for running time in the final (goal) zone of the runway, mean running times were not related to the density of these receptors (34). This indicates that differences in nonspecific locomotor activity in the runway were not related to receptor density. In contrast, measurement of cortical β-adrenoceptors after 14 once-daily extinction trials revealed a significant relationship between receptor density and the rate of extinction. However, as with the open-field paradigm, the relationship was the opposite to that anticipated. Animals with the greatest density of

TABLE 1

TREATMENTS CAUSING β-ADRENOCEPTOR DOWNREGULATION IN RAT CEREBRAL CORTEX

Stress	Duration	Reference
Immobilization	2.5 h/day; 14 days	42
	2.5 h/day; 7 days	39
	2.0 h/day; 5 days	48
Food deprivation	48 h; 6 times over 3 weeks	38
Tail-shock	1 bout/day; 5 days	22
Handling + saline injection	1 min/day; 14 days	32

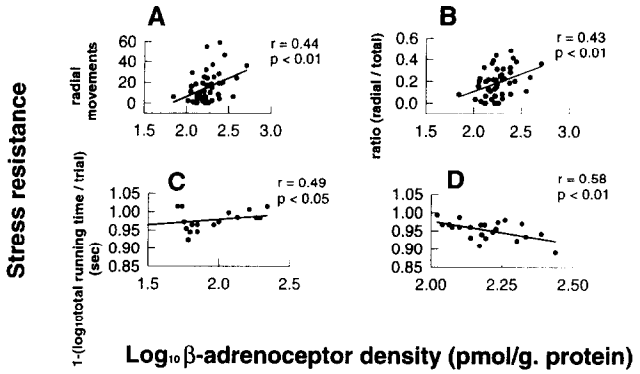

FIG. 3. Scatterplots showing the relationship between β-adrenoceptor density in rat cerebral cortex and resistance to stress: *r* values show correlation coefficients; *p* values show significance of the correlation. (A) Resistance to stress scored as radial movements over the last 3 min of a 4-min exposure to the open field. (B) Radial movements, expressed as a ratio of total (radial + arc) movements, indicating that the significance of the correlation is independent of rats' overall locomotor activity. (C) Resistance to the stress of nonreward when rats are exposed to one extinction trial per day. Stress resistance is scored as 1 − (rate of increase in total running time) during extinction in the runway. (D) Resistance to stress of nonreward during massed extinction when rats are exposed to 14 extinction trials in 1 day. Stress resistance is scored as 1 − (rate of increase in total running time) during extinction in the runway.

β-adrenoceptors showed the greatest resistance to stress (34) (Fig. 3C).

This evidence that stress resistance increases with β-adrenoceptor density conflicts with the theory that adaptation to stress involves downregulation of these receptors. One possible explanation for this disparity lies in the different types of stress used in these two series of studies. Experiments showing β-adrenoceptor downregulation used somatosensory stressors such as immobilization or foot-shock. However, the relationship between β-adrenoceptors and stress resistance in individual animals was determined after exposure to aversive naturalistic stimuli. Both the quality and intensity of these different forms of stress could therefore be key variables.

To test the impact of stress intensity, an attempt was made to intensify the animals' experience of stress without changing the total amount of stress applied. This objective is difficult to fulfill in practice. Nevertheless, a close approximation might be to repeat the experiments using nonreward but to carry out all the extinction trials on the same day (massed extinction) rather than once-daily as before. Under these conditions, the density of β-adrenoceptors correlated negatively with stress resistance such that animals with the fewest β-adrenoceptors now showed the greatest resistance to stress (21). This finding suggests that with an arguably more intense form of stress, a low β-adrenoceptor density now confers greater stress resistance (Fig. 3D).

Obviously, the complex patterns of behaviour scored in these experiments cannot be explained solely by a single neurochemical parameter: the density of β-adrenoceptors. Indeed, evidence that there is a bell-shaped relationship between receptor density and resistance to stress (cf. Figs. 3C and 3D) suggests that behaviour is governed by an interaction between β-adrenoceptors and at least one other factor. Another difficulty is that the results assume that all cortical β-adrenoceptors participate in the stress response. Measurement of changes in the response of the β-adrenoceptor second messenger system would go some way to resolving whether this is the case. This would involve measuring the amount of adenosine 3′,5′-cyclic monophosphate (cAMP) generated after activation of β-adrenoceptors by a selective agonist. If, as is assumed in the present experiments, there is no receptor reserve,

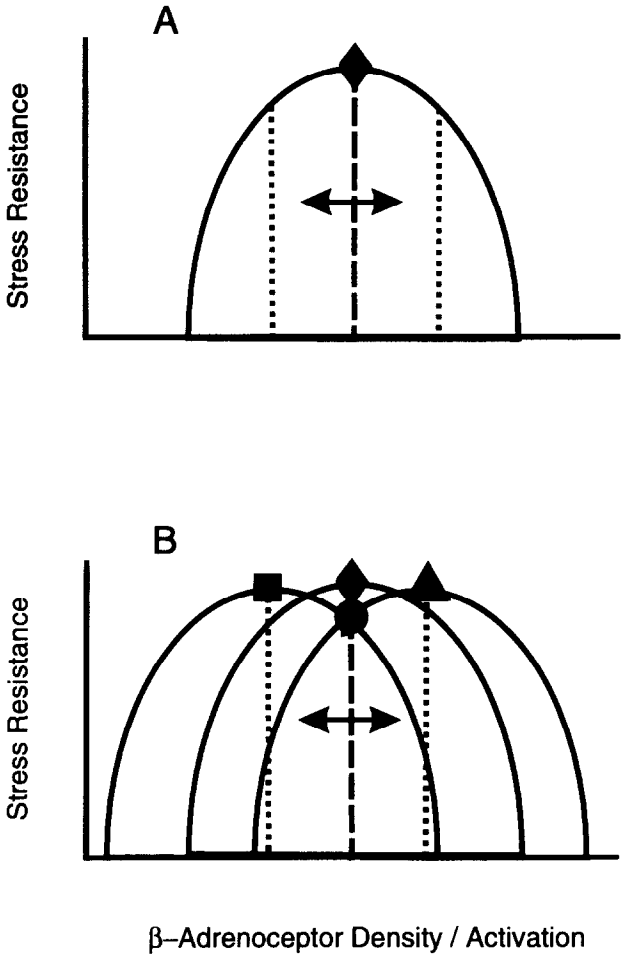

FIG. 4. Schematic diagram describing the hypothetical relationship between β-adrenoceptor density/activation and resistance to stress. (A) Maximal stress resistance results from an activation of an optimal number of β-adrenoceptors (◆); either an increase or reduction in β-adrenoceptor activation will diminish stress resistance. The impairment of stress resistance resulting from excessive receptor activation would be reversed by administration of a β-adrenoceptor antagonist. The impairment of stress resistance resulting from insufficient receptor activation would be reversed by the actions of a β-adrenoceptor agonist (e.g., an endogenous catecholamine). (B) The effects of a shift in the relationship between β-adrenoceptor density/activation and resistance to stress. At a level of β-adrenoceptor activation (---), which gives optimal stress resistance in normal subjects (◆), a shift to the right or left of the curve will diminish stress resistance (●). A further consequence of a shift to the left would be that less receptor activation would be required to produce optimal stress resistance (■). Conversely, a shift to the right would result in a need for greater receptor activation to produce optimal stress resistance (▲).

then the cAMP response should show the same correlations with behaviour as those described earlier. If they do not, this would imply that there is no causal link between individual differences in β-adrenoceptor density and behavioural responses to stress.

Despite these limitations, which are discussed in greater detail elsewhere (28,35), these studies lead to the conclusion that the role of β-adrenoceptor activation in behavioural responses to stress depends on stress intensity. If this is the case, the behavioural effects of drugs which modify the activation of β-adrenoceptors will also depend on stress intensity (Fig. 4A). It can be speculated that this might explain why certain individuals, who perceive a particular situation as unacceptably stressful seek the therapeutic support of β-adrenoceptor blockers. In contrast, the perception of stress by other individuals subjected to the same stress is that their stress response improves performance. This might be a result of the activation of β-adrenoceptors through increased release of endogenous catecholamines.

A further caveat is that a shift in the relationship between β-adrenoceptor activation and the behavioural response to stress could alter the impact of a given stress on behaviour (Fig. 4B). This might be relevant to the question of what determines differences in individuals' perception of stress intensity. Since repeated stress can cause β-adrenoceptor downregulation, individuals' stress history could be one factor which produces such a shift. Repeated administration of antidepressant drugs, which can also downregulate β-adrenoceptors, is another.

Stress History as an Experimental Variable

There seem to be no consistent changes in noradrenaline or 5-HT release after repeated stress. Some studies have found a reduction in the firing rate of noradrenergic neurones (1) and release of noradrenaline (5,29), whereas others claim that noradrenaline release is potentiated (3,30). Similarly, there are reports that 5-HT release during an acute stress challenge (indicated by changes in levels of 5-HT or 5-HIAA) is increased (3) or unchanged (23) by a previous course of repeated stress. The explanation for these conflicting reports is unknown.

The possible role of β-adrenoceptors in the stress response has already been discussed, but few studies have investigated the effects of either an acute or repeated stress on 5-HT receptors. However, recent experiments suggest that even a single stress challenge could have long-lasting effects on 5-HT_{2A} receptors. This arose from studies of neurochemical changes induced by the swim test, which involves exposing mice to a 6-min bout of swimming. Although this procedure is used as a routine preclinical screen for antidepressant agents, and has marked effects on noradrenergic neurones (44), little is known about its effect on 5-hydroxytryptaminergic transmission.

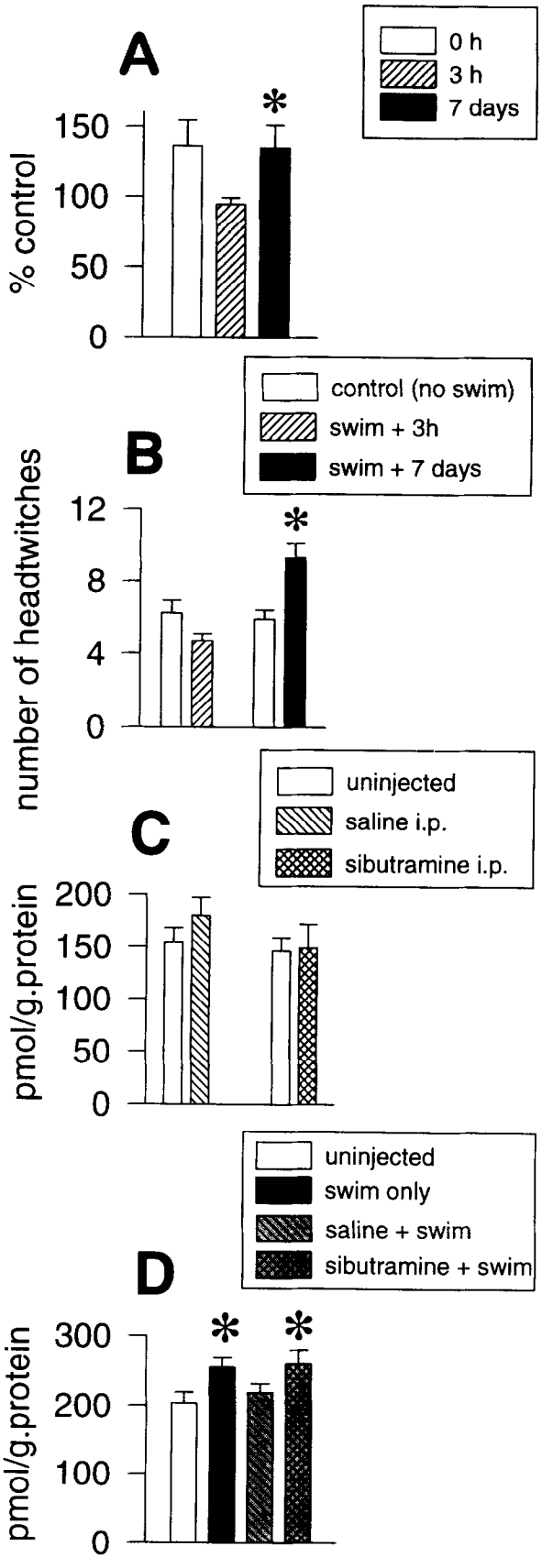

FIG. 5. The interaction between rats' history of stress or sibutramine hydrochloride on long-latency changes in receptor density and function induced by a single 6-min swim challenge. Columns show mean ± SEM. *$p < 0.05$ (Newman-Keuls test after ANOVA). Within each experiment, sample numbers (9–15) were matched across all groups. (A) Time course for changes in 5-HT_{2A} receptor density after the swim test. (B) Number of head twitches within 6 min of an IP injection of the 5-HT_2 receptor agonist 5-MeODMT. (C) Effects of 10 once-daily IP injections of saline or sibutramine hydrochloride on the density of cortical 5-HT_{2A} receptors. (D) Effects of 10 once-daily IP injections of saline or sibutramine hydrochloride on the upregulation of 5-HT_{2A} receptors found 7 days after a 6-min swim test.

Radioligand binding was carried out at various times after a 6-min swim test and focused on cortical 5-HT_{2A} receptors, because these, like β-adrenoceptors, are thought to be predominantly postsynaptic in the brain (20). The increase in cortical 5-HT_{2A} receptor density immediately after the swim test just failed to reach significance. There was also no change in binding 3 h after the swim test. However, there was a significant (25%) increase in receptor density 7 days later (Fig. 5A) (15). This increase in receptor density was paralleled by a significant (57%) increase in the frequency of head twitches induced by administration of the 5-HT_{2A}-receptor agonist, 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) (Fig. 5B). This procedure is used as an index of 5-HT_{2A} receptor function in vivo (19).

The changes in receptor density and function were both highly susceptible to animals' history of stress. This was investigated by giving mice a course of 10 once-daily saline injections followed by the swim test on the day after the last injection. Repeated injection of saline had no effect on the density of 5-HT_{2A} receptors (Fig. 5C). However, this procedure prevented the increase in receptor density and agonist-induced head twitches 7 days after the swim test (Fig. 5D) (15).

Finally, it is well established that drugs which modify noradrenergic transmission alter the latency and duration of the characteristic immobility which develops during the swim test (24). Experiments thus investigated whether repeated administration of sibutramine hydrochloride affected 5-HT_{2A} receptor upregulation after the swim test. This compound is an inhibitor of neuronal uptake of both noradrenaline and 5-HT (11). When given on a schedule which reduces immobility in the swim test (3 mg/kg, once daily for 10 days), this compound had no effect on the density of 5-HT_{2A} receptors (15) (Fig. 5C). Also, in the presence of this drug as in its absence, there was a significant upregulation of 5-HT_{2A}-receptors 7 days after the swim test (Fig. 5D). However, it should be remembered that sibutramine was itself administered by intraperitoneal (IP) injection, and yet injections of saline abolished the upregulation of 5-HT_{2A} receptors after the swim test. These results suggest that sibutramine prevents the inhibition by stressful IP injections of the upregulation of 5-HT_{2A}-receptors.

The findings from these studies emphasize the importance of animals' history of stress and drug treatment on long-lasting neurochemical effects of an acute stress challenge. Furthermore, they illustrate the potential for second-order effects on behaviour and monoaminergic transmission which are determined by the interaction between drug treatment and stress history.

CONCLUSIONS

In all of these studies, it is evident that the subjects' history of stress, as well as qualities of concurrent stress, can have marked effects on monoaminergic function in the brain. Moreover, coding of the quality or intensity of stress by monoaminergic transmission involves both pre- and postsynaptic processes. Presynaptically, changes in noradrenaline efflux show a graded response to environmental stimuli; both the magnitude and duration of the response are determined by the prevailing stimulus. Postsynaptically, the density of β-adrenoceptors correlates with behavioural responses to stress, but the precise relationship between these neurochemical and behavioural measures also depends on features of the stress, possibly its intensity. Finally, much has to be learned about the duration of changes induced by an acute stress challenge. However, it seems that changes in 5-HT_{2A} receptors, at least, can be long-lasting. Such changes could well be relevant to the prolonged effects of a single traumatic stimulus in humans, expressed as posttraumatic stress disorder. In addition, interactions between a history of stress and psychotropic drugs can have nonadditive effects on neurochemical changes induced by an acute stress challenge. These findings underline the complexity of the stress response and the inherent problems when designing experiments to investigate the effects of neurochemical and behavioural changes caused by stress and psychotropic drugs. In particular, they highlight the need to investigate interactions between psychotropic drugs and enduring effects of stress. Such investigations should include parallel studies of differences in neurochemical and behavioural responses to stress in individual animals. Only then will it be possible to test theories of causal links between changes in neurotransmission and behavioural responses induced by the types of stress known to provoke anxiety and depression in humans.

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