Pharmacology Biochemistry and Behavior, Vol. 46, pp. 511–517, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Escape Deficits Induced by Uncontrollable Foot-Shock in Recombinant Inbred Strains of Mice

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Received 24 November 1992

SHANKS, N. AND H. ANISMAN. *Escape deficits induced by uncontrollable foot-shock in recombinant inbred strains of mice.* PHARMACOL BIOCHEM BEHAV **46**(3) 511–517, 1993. – Although uncontrollable stressors reliably induce numerous behavioral disturbances, considerable interindividual variability exists in this respect. Inasmuch as genetic factors may be fundamental in determining vulnerability to stressor effects, the present investigation assessed alterations in escape performance following exposure to uncontrollable foot-shock in the BALB/cByJ and C57BL/6ByJ mice and seven recombinant inbred strains. Exposure to uncontrollable foot-shock disrupted shuttle escape performance in a strain-specific manner; however, any differences due to gender were not particularly remarkable. The profile of stressor effects in the recombinant strains (i.e., performance deficits greater, lesser or intermediate to the progenitor strains) suggest that the stressor effects on escape performance may be subserved by two or more genetic determinants. The findings are related to central mechanisms that may potentially account for strain differences.

Stress Genetics Recombinant strains

THE effectiveness of stressors in modifying behavior, as well as neuroendocrine and neurotransmitter activity, is influenced by a number of factors relating to the stressor itself (e.g., the intensity, duration, controllability, predictability, and chronicity) and experiential factors (e.g., animals' previous history with similar or dissimilar stressors), as well as the environmental backdrop upon which a stressor was superimposed (e.g., housing conditions) (1,3). In addition, it appears that the response to stressors varies with organismic variables, such as the age of the organism, as well as the species or strain being examined (11,12,23,24,39).

In view of the large number of variables that influence the response to stressors, it is not surprising that considerable interindividual variability exists with respect to the behavioral disturbances associated with uncontrollable aversive events (36,43). It has been assumed that the variability in the behavioral response to stressors is determined by the individual differences in the neurochemical and endocrine changes associated with aversive events (3). One potentially useful strategy to identify the correspondence between the behavioral effects of stressors and the alterations of endogenous endocrine and transmitter activity is the use of inbred strains of mice, which exhibit different behavioral or neurochemical profiles in response to environmental insults. Several recent experiments conducted in our laboratory have revealed that marked differences exist across strains of mice with respect to the effects of an uncontrollable stressor on plasma corticosterone concentrations, as well as the utilization and levels of norepinephrine (NE) and dopamine (DA) in several brain regions (42,43). As well, appreciable strain differences were observed with respect to stressor-provoked behavioral disturbances in several paradigms, including shuttle escape performance, responding for electrical brain stimulation from various brain regions, consumption of a highly palatable diet, and behavior in an exploratory paradigm (17,19,41,49,50,51). In general, vulnerability to a stressor-induced performance deficit in one behavioral paradigm was not necessarily predictive of disruption in a second paradigm. Nevertheless, it did appear that the BALB/cByJ mouse was particularly vulnerable to the impact of stressors. In particular, BALB/cByJ not only exhibited the greatest increase of plasma corticosterone following foot-shock but also displayed prominent alterations of mesocorticolimbic DA activity, as well as variations of NE within the hypothalamus and locus coeruleus (14,21,43). Paralleling these findings, BALB/cByJ mice exhibited particularly marked stressor-induced behavioral disturbances in a shuttle escape task, in performance in both an exploratory and water maze task, in responding for electrical brain stimulation from the prefrontal

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cortex, and in consumption of a highly palatable liquid diet. In contrast, the C57BL/6J mouse appeared to be less vulnerable to both the behavioral effects of stressors and plasma corticoid alterations, and the central NE and DA reductions engendered by stressors were generally modest relative to that seen in BALB/cByJ mice (12,43).

Given the particular vulnerability of the BALB/cByJ strain to stressor-induced behavioral disturbances, the present investigation was conducted to evaluate further the effects of inescapable shock in BALB/cByJ mice and in the hardier C57BL/6ByJ strain, as well as in seven recombinant inbred strains derived from these progenitor strains. Recombinant inbred strains of mice may be useful in determining whether a particular phenotype involves a single gene and may be well suited to determine the mechanisms that subserve a given behavioral phenotype. The recombinant strains were originally derived from the cross of the highly inbred progenitor strains, followed by strict inbreeding from the F2 generation. The continued inbreeding fixed the chance recombinations of genes from the original parent strains in a homozygous state (5). If a particular phenotype is determined by a single gene effect, then each of the recombinant strains should resemble either one parent strain or the other. Numerous studies that have been conducted using the recombinant strains have revealed, among other things, wide between-strain variability in exploratory behavior (35), performance in learning tasks (44), wheel-running activity (16), circadian rhythms of locomotor activity (7,37), saccharin preference (48), hippocampal morphology (34), tyrosine hydroxylase activity (47), uptake of NE, choline, and GABA (40), basal corticosterone levels (15), and responses to drugs such as morphine (13,33), as well as the presence of opioid binding sites in the brain (31,32). In the present investigation, we assessed the impact of uncontrollable foot-shock on shuttle escape performance in the recombinant inbred strains of mice. Typically, shuttle escape deficits are apparent when animals are tested soon after exposure to inescapable shock of moderate intensity and tend to become more pronounced over the 24-h period following stressor exposure (41). Because our intention is ultimately to relate the behavioral effects of stressors in these strains to the short-lived catecholamine alterations engendered by uncontrollable stressors, in the present investigation performance was assessed soon after inescapable shock.

METHOD

Subjects

A total of 366 mice of the nine strains (n = 39–49/strain), approximately 60 days of age, served as experimental subjects. Mice were bred in this laboratory from parent stock obtained from the Jackson Laboratory (Bar Harbor, ME). Pups were kept with the dam until they were 21 days of age, at which time they were sexed and housed in groups of three to five. Mice were maintained on a 12 L : 12 D cycle (light on 0700–1900 h) and were tested between 0830 and 1200 h.

Apparatus

Inescapable foot-shock was administered in six black Plexiglas chambers that measured 30.0 × 14.0 × 15.0 cm. The chamber floors consisted of 0.32-cm stainless steel rods spaced 1.0 cm apart (center to center) and connected in series by neon bulbs. The end walls of the chambers were lined with stainless steel plates and were connected in series to the grid floor. Shocks were delivered to the floors through a 3,000-V source. Red Plexiglas roofs served to reduce illumination of the chambers.

Shuttle escape testing was conducted in four identical black Plexiglas shuttle boxes, which measured 29.2 × 8.9 × 16.5 cm. Each shuttle box was divided into two compartments by a black Plexiglas wall and horizontally movable gate. When the gate was open, a hurdle 1.27 cm in height separated the two compartments and a 5.2 × 6.1 cm space permitted access into the adjacent compartment. The hurdle was lined with stainless steel plates that were connected in series with the grid floor, which thereby prevented mice from avoiding a shock by sitting on the hurdle. Situated 1.1 cm on either side of each hurdle were two infrared photocells, 1.27 and 2.54 cm above the grid floor, respectively. The photocells were wired so that if the beams on both sides of the hurdle were crossed simultaneously, as might occur when the mouse was halfway through the gate, the cells did not trigger. When the mouse crossed the beam in the shock compartment and broke the beam on the safe side only, the cell was triggered. An additional set of photocells were located 2.54 cm from the end walls. If a mouse did not trigger the first set of cells (e.g., if the mouse jumped over the cells), these latter cells were triggered. All boxes were housed in sound-attenuated chambers. The apparatus was controlled by a microcomputer system constructed by Carleton University Science Workshops, and latencies to respond were recorded independently for each of the shuttle boxes.

Procedure

Animals of each strain were randomly assigned to either the shock or no-shock treatment groups. Half of the mice of each strain were placed in the shock chambers and exposed to 360 shocks of 2-s duration (150 mA, AC) at 9-s intervals. The nonshocked controls of each strain were exposed to the apparatus for an equal amount of time (1.1 h) but shock was withheld. The number and severity of uncontrollable shock presentations used in this investigation had previously been found to be effective in inducing behavioral deficits in a number of inbred strains, as well as in the CD-1 outbred mouse strain, and has been shown to reduce central NE and DA concentrations in these mice (1,42,43). In contrast, escapable shock involving the same parameters has routinely been found not to affect either escape performance or central NE concentrations (3). Immediately after pretreatment, animals were placed individually in the shuttle apparatus and given 30 shuttle escape trials at intervals of 30 s (150 mA). In the first five trials, the gate separating the two compartments opened simultaneously with shock onset. In the latter 25 trials, the gate did not open until 4 s after shock onset. Each trial was terminated as soon as the mouse crossed a photocell in the adjacent compartment. If an escape response was not made, the trial terminated 24 s after the gate was opened.

RESULTS

The mean escape latency in male and female mice of each strain, as a function of the stressor treatment, is illustrated in Figs. 1 and 2, respectively. Analysis of variance of escape latencies revealed that shuttle performance varied as a function of the strain × shock × blocks of trials interaction, $F(32, 1{,}320) = 1.99$, $p < 0.01$, as well as the strain × sex × blocks interaction, $F(32, 1{,}320) = 1.67$, $p < 0.05$. As seen in Fig. 1, and confirmed by Newman–Keuls multiple comparisons ($\alpha = 0.05$) of the simple effects comprising the latter interaction, escape latencies were shorter in C57BL/6ByJ than in BALB/cByJ mice. CXBE, CXBH, and CXBJ mice exhib-

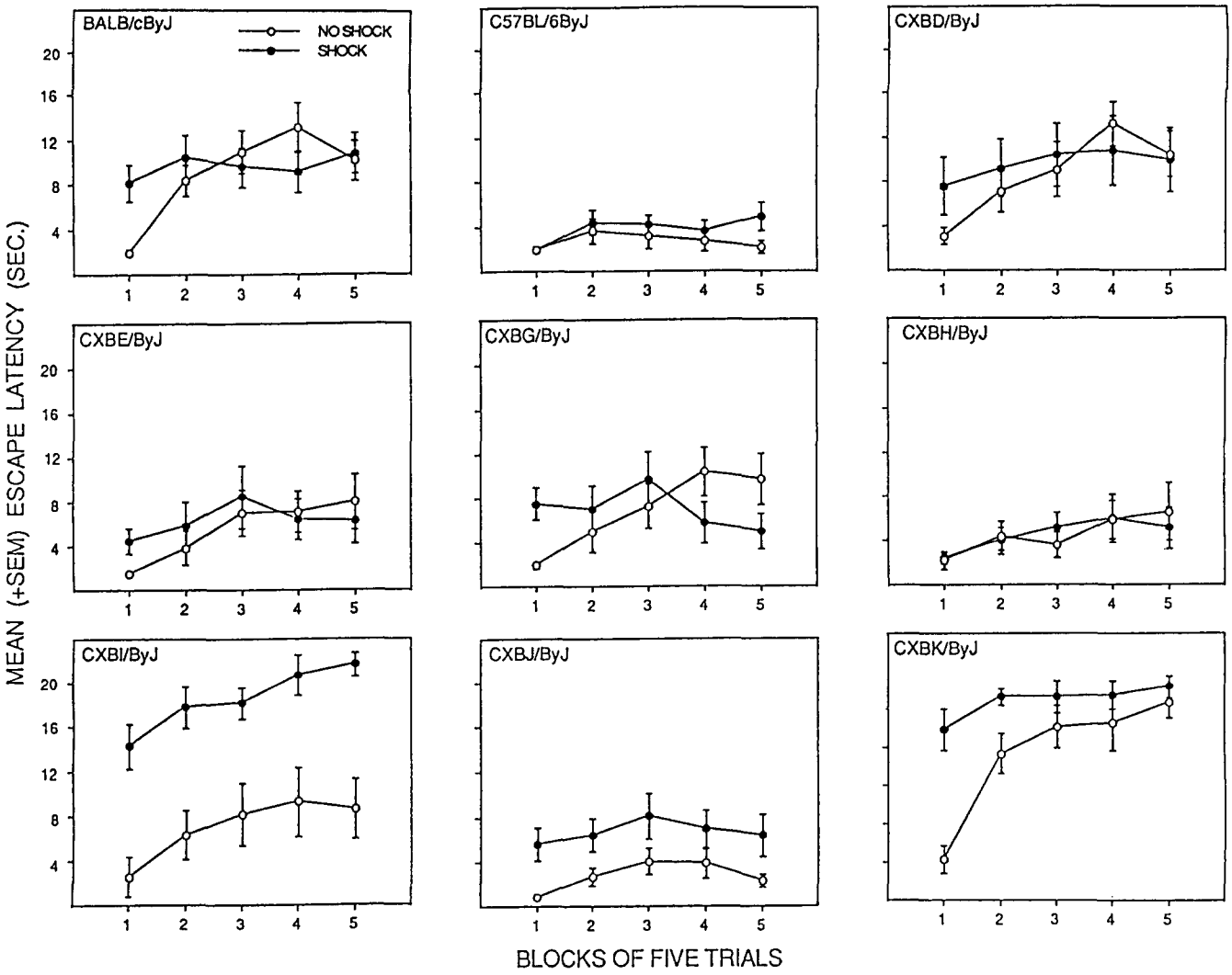

FIG. 1. Mean (± SEM) latency to escape (seconds) across five blocks of five trials in male progenitor (BALB/cByJ and C57BL/6ByJ) and recombinant inbred mouse strains following exposure to either uncontrollable foot-shock or no shock exposure.

ited latencies comparable to that of the C57BL/6ByJ progenitor and significantly shorter than that of the BALB/cByJ progenitor, while CXBD and CXBG mice exhibited latencies comparable to BALB/cByJ mice. Latencies significantly longer than those of BALB/cByJ mice were evident in the CXBI and CXBK strains. Differences between male and female mice were limited, with male C57BL/6ByJ mice displaying shorter escape latencies during the latter portions of the test session than females. Moreover, CXBD males exhibited faster latencies than females of this strain during the second and third trial blocks.

Newman-Keuls multiple comparisons of the shock × strain × blocks interaction indicated that the inescapable shock treatment did not affect the performance in C57BL/6ByJ mice of either sex, just as such a treatment was previously shown to provoke little effect in the C57BL/6J strain (41). In contrast, the inescapable shock treatment produced a disturbance of performance in BALB/cByJ mice, but this effect was restricted to the early training trials. As previously observed, over blocks of trials the performance of BALB/cByJ mice deteriorated markedly, while in C57BL/6ByJ this deterioration was less pronounced. Among the recombinant strains, several distinct behavioral profiles were apparent in response to the inescapable shock treatment. In particular, in nonshocked CXBI mice performance was reminiscent of that seen in BALB/cByJ mice but inescapable shock produced a marked deterioration of performance, such that latencies were slower than in BALB/cByJ mice. Likewise, in CXBK mice performance was disrupted by inescapable shock to a far greater degree than in BALB/cByJ mice; however, in nonshocked mice of this strain a marked deterioration (beyond that of the BALBs) of performance over trials was observed. In contrast, the performance of CXBG mice was similar to that of BALB/cByJ mice, while that of CXBE and CXBJ was similar to that of C57BL/6ByJ mice. Finally, the performance of CXBH mice could be differentiated from either of the original progenitor strains. In male CXBH mice, rapid escape latencies were apparent and performance was not affected by the prior inescapable shock treatment. In female mice of this strain, rapid escape latencies were likewise evident and the

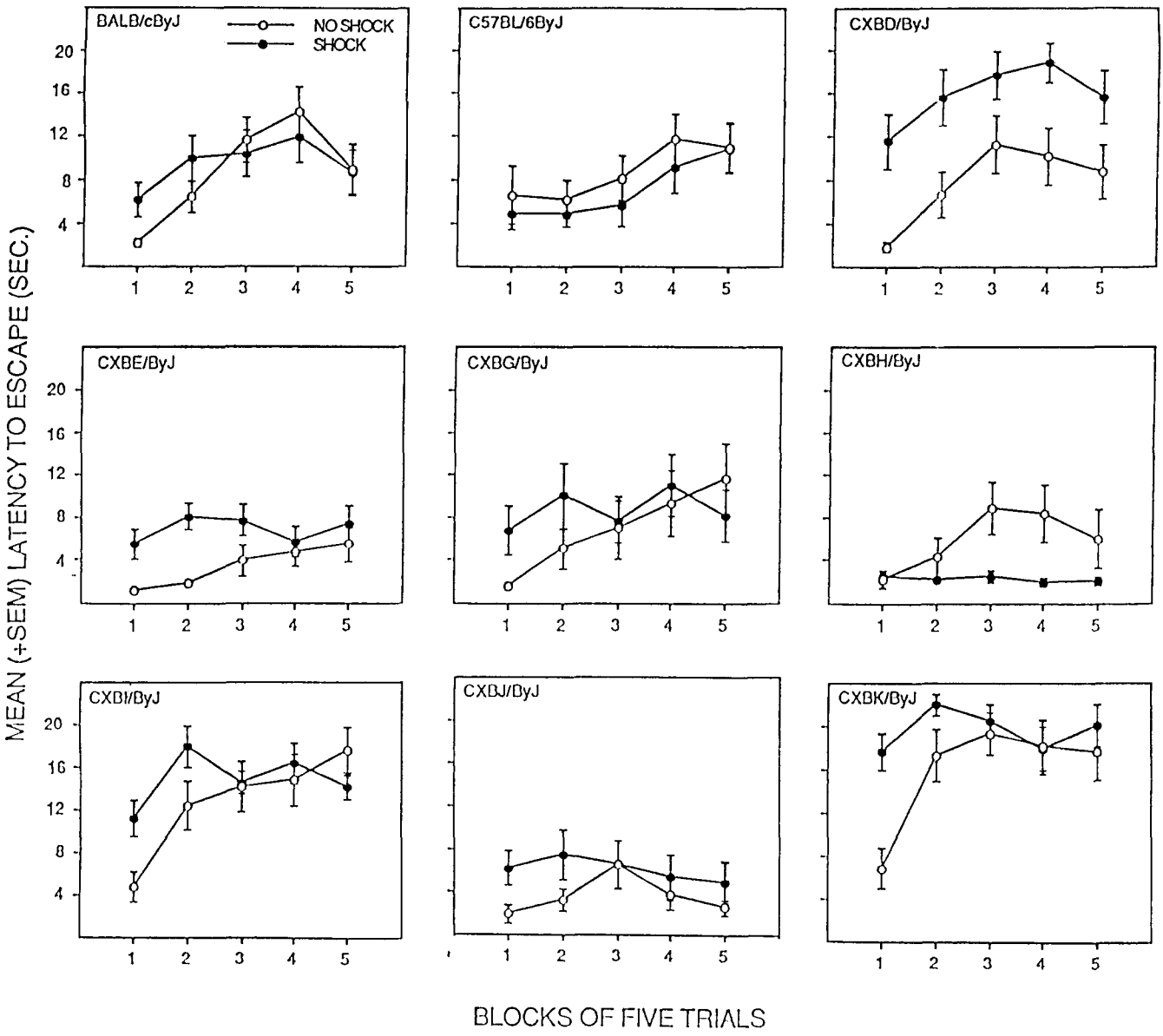

FIG. 2. Mean (± SEM) latency to escape (seconds) across five blocks of five trials in the female progenitor (BALB/cByJ and C57BL/6ByJ) and recombinant inbred mouse strains following exposure to either uncontrollable foot-shock or no shock exposure.

inescapable shock treatment provoked a significant facilitation of escape performance. Only in CXBD mice was the inescapable shock found to have a sex-dependent effect. In males, a small disruption of performance was induced by inescapable shock, while in females this effect was particularly marked. However, it is important to note that it has recently been discovered that the recombinant inbred CXBD/By line of the CXB recombinant lines was genetically contaminated (at the Jackson Breeding Laboratory) some time in 1989. Because our breeding stock was obtained from Jackson Laboratories during this time period, contamination may have contributed to the gender- or strain-specific behavioral profile of the CXBD/ByJ strain.

DISCUSSION

It will be recalled that the escape deficits typically engendered by a stressor of modest severity are more pronounced 24 h after inescapable shock than immediately after such a treatment (2,18). It has been argued that soon after inescapable shock treatment heightened arousal may compete with response initiation and response maintenance disturbances that otherwise favor retarded escape latencies (3,38). Alternatively, it is possible that the passage of time itself in some fashion influences central neurotransmitter activity, or the responsivity to subsequent environmental challenges, thereby leading to a time-dependent enhancement of the behavioral disturbances (4). At any rate, earlier studies had, in fact, confirmed that the escape deficits induced by uncontrollable foot-shock in the BALB/cByJ strain was less marked immediately after inescapable shock treatment than at a 24-h interval (41). Commensurate with these earlier findings, in the present investigation where performance was assessed soon after inescapable shock the magnitude of the escape deficit in the BALB/cByJ strain, although statistically significant, was not

particularly marked. Thus, in assessing the performance of the recombinant inbred strains it was of interest not so much to evaluate whether absolute response latencies resembled that of one parent strain or the other but rather whether inescapable shock in the recombinant strains provoked performance deficits as in the BALB/cByJ parent strain or had no effect as in the C57BL/6ByJ strain.

As previously reported, inescapable shock elicited marked disturbances of escape performance, but the occurrence of the performance disruption varied across strains of mice. In some of the recombinant strains, the performance deficits resembled those seen in the BALB/cByJ progenitor, while other strains exhibited proficient escape behavior resembling C57BL/6ByJ mice. As well, it was clear that in some strains the inescapable shock provoked deficits more pronounced than either of the parent strains, or alternatively the stressor treatment provoked an enhancement of performance. As such, these data suggest that two or more genetic determinants subserve the stressor effects on shuttle escape performance.

In contrast to earlier reports (45,46), marked sex differences in escape performance following stressor exposure were not apparent in the present investigation. In most instances, performance between the two genders was equivalent, with the exception of CXBD/ByJ mice. The source for the inconsistency between the present observations and previous reports is not readily apparent given the appreciable procedural differences between studies, including the differences in the species being examined, as well as the characteristics of the behavioral tests used. Steenbergen et al. (45,46) had suggested that gender differences in motoric behaviors in response to a stressor may account for the sex differences in escape performance following exposure to an inescapable stressor. Although we have likewise argued that motoric factors play a prominent role in accounting for the behavioral differences engendered by inescapable shock (3), it is conceivable that among inbred strains of mice gender accounts for only a small proportion of the variance with respect to disturbances of response initiation and maintenance. This is not to say that inbred strains do not vary in their response styles, but rather that the behavioral repertoires adopted following stressor exposure (i.e., jumping, running, freezing), and hence the escape proficiency, are consistent in male and females in any given strain.

The strain profile of shuttle escape performance in the present investigation could be distinguished from other behaviors observed in these strains, including wheel running and locomotor activity [cf. (9,16,37)], as well as basal values of corticosterone (16). Interestingly, the pattern of results was similar to the strain differences that have been reported with respect to opiate binding sites. In particular, it was demonstrated that CXBK mice have fewer opiate binding sites, particularly of the M_1 variety, than either of the progenitor strains, which in turn are lower than those of CXBH mice (6,32). Moreover, CXBK mice exhibited less evidence of analgesia following administration of either morphine (33) or stressor application (30), as well as the naloxone-induced reversal of analgesia produced by electrical stimulation of periaqueductal gray matter (31). Given the correspondence between the performance changes observed after inescapable shock in the present experiment (marked disruption in CXBK and either facilitation or no effect in CXBH), the possibility should be entertained that the performance changes in these strains may be related to the distribution of opiate receptors. Yet, it should be considered that while CXBI mice exhibited pronounced performance deficits, at least as marked as those of CXBK mice, opiate receptor density and the analgesic response to morphine in CXBI mice was comparable to that of the two progenitor strains (6). Of course, several different mechanisms have been implicated in the mediation of stressor-induced behavioral deficits, including central changes of NE, DA, and 5-hydroxytryptamine (5-HT), as well as acetylcholine (ACh) (3), and hence the mechanisms operative in provoking a given behavioral disturbance in one strain need not be the same as that associated with a comparable behavioral disturbance in a second strain.

It should be underscored that we are not arguing that deficits of escape performance are subserved by stressor-induced alterations of opiate activity. Although those manipulations that influence the development of a stressor-related analgesia also favor the appearance of shuttle escape deficits, including stressor controllability (22), and the specific schedule of shock presentations (29), there are data indicating that modification of the analgesia does not influence the stressor-induced shuttle deficits. For instance, both hypophysectomy and dexamethasone treatment eliminate the stressor-induced analgesia but do not affect the disturbances of shuttle escape performance (27), and neither treatment with naloxone nor morphine affected the stressor-provoked shuttle escape deficits (28). Maier et al. (29) have argued that while the analgesia induced by inescapable shock is not responsible for the escape interference the two may have some common underlying features or that those manipulations that lead to endogenous chemical changes subserving the analgesia also lead to neurochemical or endocrine changes that subserve the escape deficits. Our position is not unlike this proposition, although the possibility ought to be entertained that the contribution of a stressor-induced opiate release and the ensuing analgesia may differentially influence shuttle performance across strains of mice. Further, given that opioid activity has been shown to influence or interact with transmitters such as norepinephrine and dopamine (8,20, 25,26) the possibility should be entertained that the strain differences in performance may be related to complex interactions between opiates and other neurotransmitters. We are presently assessing the effects of stressors on plasma corticoid and brain catecholamine concentrations and turnover in the recombinant strains to determine other correlates of the stressor provoked behavioral impairments.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of Bob Rinfret. This work was supported by Grant MT6486 from the Medical Research Council of Canada.

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