Pharmacology Biochemistry and Behavior, Vol. 42, pp. 219–227, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Strain-Specific Alterations in Consumption of a Palatable Diet Following Repeated Stressor Exposure

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Received 27 November 1991

GRIFFITHS, J., N. SHANKS AND H. ANISMAN. *Strain-specific alterations in consumption of a palatable diet following repeated stressor exposure.* PHARMACOL BIOCHEM BEHAV **42**(2) 219–227, 1992.—Exposure to acute inescapable shock caused reductions in the consumption of a highly palatable diet. The magnitude and duration of the reduction varied across strains of mice. With repeated exposure to footshock, consumption of the diet returned to baseline levels, although alterations of weight appeared to be more persistent. The course of the adaptation varied across strains of mice; however, the rate of adaptation was unrelated to the extent of the alterations of consumption induced by the acute stressor. When mice were exposed to a series of different stressors, the adaptation progressed less readily, and reductions of diet consumption were apparent in strains that had not shown such an effect following acute stressor application or when repeatedly exposed to a single type of stressor. Data were discussed with respect to the mechanisms that might be operative in subserving stressor-induced anhedonia.

Stress Anhedonia Feeding Genetics

IN support of the contention that stressors promote or exacerbate symptoms of depression, it has been shown that environmental stressors will, among other things, result in anhedonia (4,25). For instance, exposure to an uncontrollable footshock markedly reduced responding for rewarding brain stimulation when electrodes were positioned in mesocorticolimbic structures, including the prefrontal cortex, nucleus accumbens, and ventral tegmentum (30–33). In contrast, responding for stimulation from nigrostriatal structures was unaffected by stressor exposure (28). Because stressors have more profound effects on mesocorticolimbic than nigrostriatal dopamine (DA) activity, it was suggested that variations of DA activity contribute to the stressor-provoked behavioral disturbances (4,25). Indeed, it was demonstrated that with repeated stressor application the disruption of self-stimulation responding was attenuated, just as the reductions of DA were minimized (10). Finally, repeated administration of the tricyclic antidepressant, desmethylimipramine, effectively antagonized the stressor-induced disturbance of self-stimulation from the nucleus accumbens (26,27,29).

Paralleling these findings, it was demonstrated that aversive stimulation reduced the consumption of highly palatable diets (6,7,11,23,24). Inasmuch as this effect was observed irrespective of whether a nutritive or non-nutritive solution was used, it is unlikely that the altered consumption was caused by variations in caloric intake, but instead may have reflected a stressor-provoked anhedonia (11,24). Commensurate with the effects of footshock on responding for brain stimulation, the effects of the stressor on consumption of the palatable diet diminished with repeated exposure to a given stressor (12). However, a marked and persistent reduction in the intake of a palatable substance (saccharin or sucrose) was induced when animals were exposed to a series of different stressors over successive days (14,24). Moreover, this effect, like the alterations in responding for brain stimulation, could be antagonized by repeated treatment with clinically effective antidepressant agents (11,13,23).

Although behavioral disturbances are engendered by stressors in a wide variety of behavioral paradigms, considerable interindividual variability exists in this respect. While some animals exposed to an uncontrollable stressor subsequently display repeated failures to learn or to perform a particular response, other animals are seemingly unaffected by the treatment (5). Likewise, it has been demonstrated that marked interstrain differences exist with respect to the behavioral effects of stressors. However, the development of disturbances in one paradigm does not necessarily assure a disturbance in a second paradigm. For instance, DBA/2J mice exposed to inescapable shock exhibited proficient shuttle escape performance but displayed deficits in responding for electrical stimu-

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lation from the nucleus accumbens (16,33). Like the stressor-induced behavioral changes, it has been reported that neurochemical alterations engendered by stressors also vary across strains of mice. Moreover, it appears that the brain regions in which the transmitter alterations are most pronounced are strain-specific as well (19). Thus, as in the case of the behavioral changes, it is inappropriate to consider the strains as being relatively vulnerable or invulnerable to stressor-provoked neurochemical alterations, although the BALB/cByJ mice have been noted to be more readily affected by stressors relative to other strains (18,19).

Since depression may be a biochemically heterogeneous illness (20,21), analysis of animal models of the disorder ought to consider the interindividual or interstrain variability in the symptoms of the disorder. The purpose of the present investigation was to assess the effects of different stressor regimens on consumption of a highly palatable liquid diet and to determine the strain differences in this respect. In addition, the strain profiles observed in the present investigation were related to those previously observed in another test of anhedonia, namely self-stimulation performance after stressor exposure (30,33), as well as to amine alterations engendered by the stressor experience (19).

EXPERIMENT 1

The norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reductions, as well as the deficits of performance in several behavioral paradigms ordinarily associated with acute stressors, are absent following repeated exposure to a given stressor (1,9,15,22). Experiment 1 was undertaken to a) determine whether the reduction in the intake of a highly palatable diet among mice would likewise be subject to an adaptation following repeated stressor exposure, and b) assess whether strain differences would be evident in this respect.

METHOD

Subjects

A total of 24–40 naive male mice of each of five inbred strains (A/J, BALB/cByJ, C57BL/6J, C3H/HeJ, and DBA/2J) and one outbred strain (CD-1) served as subjects in this experiment. The five inbred strains were obtained from the Jackson Laboratory (Bar Harbor, ME), while the noninbred CD-1 mice were obtained from Charles River Inc. (St. Constant, Quebec), at 45–50 days of age. The mice were permitted approximately 2 weeks to acclimatize to the laboratory prior to serving as experimental subjects. During the acclimatization, the mice were housed in groups of five in standard polypropylene cages, maintained on a 12 L : 12 D cycle, and permitted free access to food and water. These particular inbred strains of mice were chosen because they were previously shown to reflect a wide range of responses to stressors in terms of several behaviors (16,33), neurochemical activity (19), corticoid secretion (18), and in response to antidepressant agents (17). As noted earlier, the CD-1 strain was included for comparative purposes and also because most of the work of a nongenetic nature conducted in this laboratory has involved this strain.

Apparatus

Inescapable footshock was administered in six black Plexiglas chambers which 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. Shock was delivered to the grid floor through a 3000-V source. Red Plexiglas covers reduced illumination of the chambers.

The liquid diet used in the present investigation consisted of a mixture of Ensure (Abbott Laboratories, Montreal, Quebec) (35.6%), Enrich containing fibre (Abbott Laboratories, Montreal, Quebec) (13.4%), and distilled water (51%). Preliminary studies performed in this laboratory indicated that this particular diet was readily consumed, and over the course of several weeks no ill effects of the diet were noted. Moreover, when permitted access to this diet for restricted periods during the day, mice readily consumed large amounts (7 cc over 2 h), even though they had ad lib access to food pellets. Moreover, when given a choice between the liquid diet and standard food pellets, mice exhibited a marked preference for the former. Indeed, under this condition mice almost invariably ignored the food pellets. These findings were taken to suggest that mice consumed this diet for its hedonic value. Parenthetically, the novelty of the diet was not responsible for the increased intake, since mice required several days of adaptation to the Ensure-Enrich before they exhibited high and stable rates of intake.

Procedure

In Experiment 1 the mice were individually housed and given a 2-week period to acclimatize to the liquid diet such that stable consumption (within 12% variation) was established. The diet, as well as water, was available ad lib, except during the period when the diet bottles were changed (between 0730–1500 h). Following the 2-week acclimatization period, mice were assigned to one of three treatment groups matched on the basis of liquid diet consumption and body weight averaged over the final 3 baseline days. The animals were then exposed to either chronic or acute footshock or simply placed in the apparatus without shock being delivered. The acute footshock treatment consisted of mice being exposed to 360 footshocks (300 μA) of 2-s duration at intervals of 9 s, while the chronic footshock condition consisted of this treatment being applied daily for 14 consecutive days. The nonshocked animals were exposed to the apparatus on a daily basis for the 14 days of the treatment regimen. All body weights were obtained prior to shock exposure.

RESULTS AND DISCUSSION

The mean liquid diet consumption, as a percentage of control values, for each of the groups is shown in Fig. 1. Analysis of variance (ANOVA) of the scores revealed that intake varied as a function of the Strain × Stressor × Days interaction, $F(130, 2340) = 1.23, p < .05$. Newman-Keuls multiple comparisons of the simple effects comprising the interaction ($\alpha = 0.05$) confirmed that in nonshocked mice, irrespective of the strain, consumption remained relatively stable throughout the testing period. Exposure to acute shock induced a transient reduction in consumption, which was evident only on the first test day in CD-1, DBA/2J, C57BL/6J, and BALB/cByJ mice, on both days 1 and 2 in C3H/HeJ mice, but absent entirely in the A/J strain. The extent of the reductions induced by the acute stressor was also found to vary across strains of mice. For instance, in the CD-1, DBA/2J and BALB/cByJ strains the proportion of baseline consumption was lower than in the C57BL/6J and C3H/HeJ mice, which in turn was lower than that seen in A/J mice.

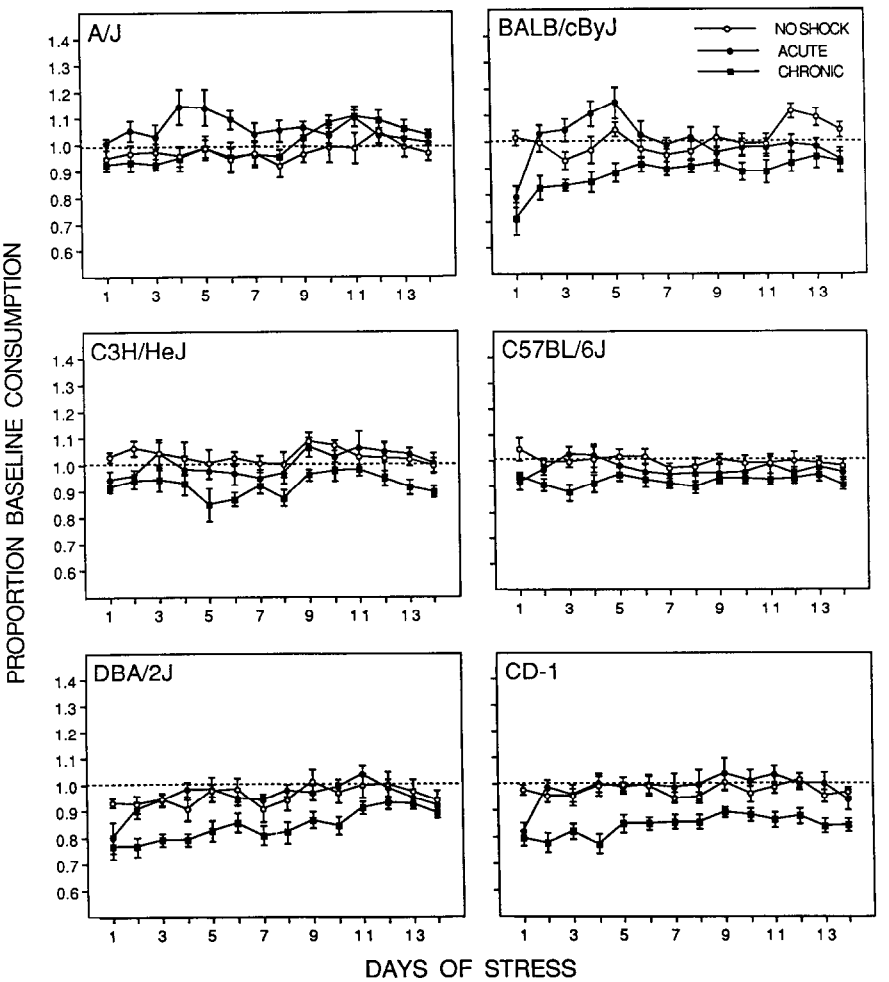

FIG. 1. Mean (±SEM) proportion of baseline consumption of a palatable liquid diet following either acute or chronic stressor exposure, or exposure to apparatus in six strains of mice.

The chronic stressor treatment reduced food intake more persistently, but in each strain some recovery of consumption was evident over the course of the test period. In the DBA/2J mice the stressor significantly reduced the consumption of the diet, and not until day 11 did intake levels reach that of nonstressed animals. In CD-1 mice consumption was curtailed by the stressor throughout most of the test period, with the exception of days 9 and 10 when intake did not differ from nonstressed animals. In the remaining strains the decline in consumption associated with the stressor was less protracted, being evident only until days 3, 5, and 6 in the C57BL/6J, BALB/cByJ and C3H/HeJ mice, respectively. In the A/J mice, consumption of the liquid diet was unaffected by the stressor.

Weight changes, like food intake, were found to vary as a function of the Strain × Shock treatment × Days interaction, $F(130, 2340) = 1.38$, $p < 0.05$. As seen in Fig. 2, and confirmed by the Newman-Keuls multiple comparisons ($a = 0.05$), in nonstressed mice weight increased over the course of the 14-day test period. This was to be expected since the mice were only approximately 60 days of age at the commencement of the study, and thus were still growing. The extent of the weight change that occurred over the 14 days, however, was found to vary appreciably across strains. In particular, the noninbred CD-1 mouse, which is larger than the inbred strains, displayed only a modest increase in weight (approximately 3%), while the DBA/2J and C57BL/6J mice displayed an increase of about 6–7%, which was lower than that seen in the C3H/HeJ, BALB/cByJ, and A/J mice, which exhibited weight gains that ranged from 11 to 16%.

Exposure to the acute stressor treatment provoked a small, but significant decline in weight in most strains; the time course for this weight change varied with the strain being examined. In CD-1 mice weight was reduced only after the first test session. In the A/J and BALB/cByJ strains the reductions in weight were somewhat more persistent, being apparent during days 1–3 and days 2–3, respectively. Still more persistent reductions were apparent in C57BL/6J mice, in which weight was lost during several of the early test days, as well as through days 10–13, while in the C3H/HeJ mice reductions were evident throughout testing, although this reduction in weight gain was only significant very early in testing. In contrast to the other strains, in DBA/2J mice the acute stressor treatment did not influence weight significantly.

The chronic stressor treatment provoked reductions in

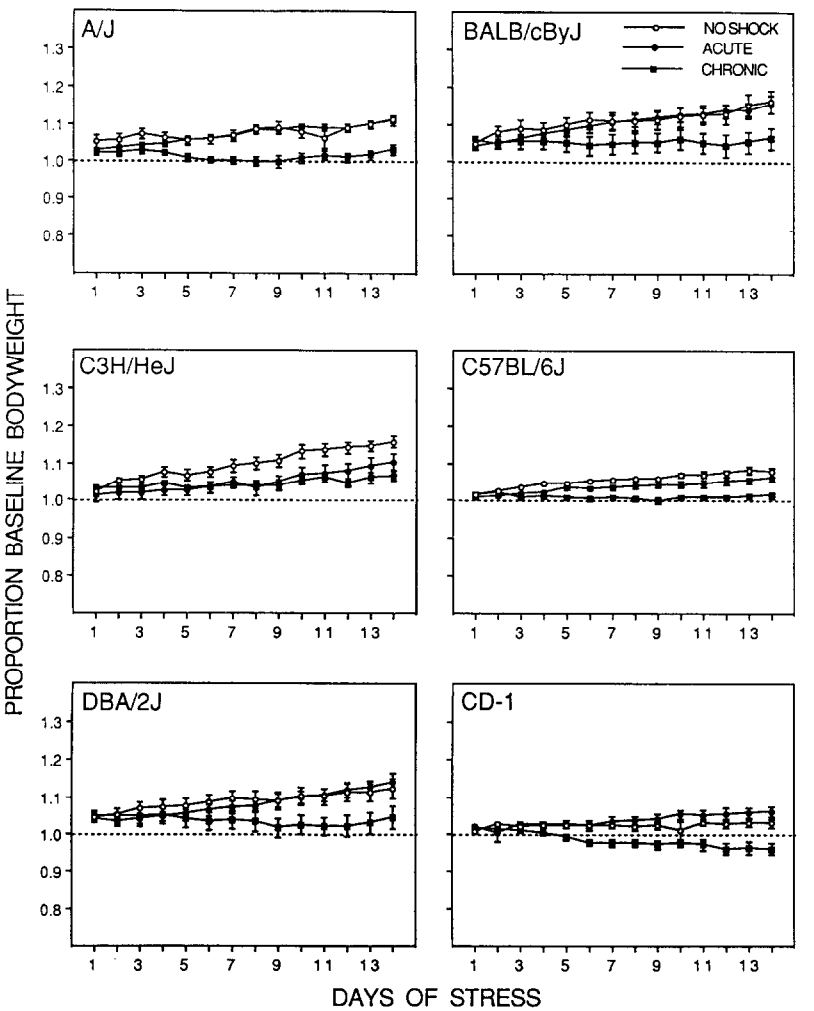

FIG. 2. Mean (±SEM) proportion of baseline bodyweights following either acute or chronic stressor exposure, or exposure to apparatus in six strains of mice maintained on a palatable liquid diet.

weight gain. However, the extent to which bodyweights were affected varied across the different strains of mice. In contrast to the weight gain ordinarily seen in CD-1 mice, animals in the chronic shock condition exhibited a small decline in weight over the course of the 14-day test session. In A/J, DBA/2J, and C57BL/6J the weight gain in stressed mice did not vary significantly from baseline over the 14 days, which contrasts with the weight gain seen in nonstressed animals of these strains. It seems that despite the adaptation observed with respect to food intake, chronic stressor exposure provoked more persistent alterations in weight. Dess, Minor, and Brewer (7) previously observed a comparable incongruence between food intake and weight change, prompting these investigators to suggest that the stressor treatment may have altered the animal's set point, thereby provoking the relatively persistent changes in weight. The fact that weight changes were induced even in the absence of alterations in food intake (as in the case of the A/J mice) suggests that the variations in weight gain were not attributable simply to changes in diet, but reflected involvement of other processes, such as sustained alterations in metabolic rate.

EXPERIMENT 2

It is clear from Experiment 1 that inescapable footshock provoked a reduction in the voluntary consumption of a highly palatable diet. Adaptation occurred with repeated exposure to the stressor, so that consumption was ultimately equivalent to that of nonstressed animals. As in the case of other stressor-provoked behavioral changes, it appeared that the extent of the initial decline in food intake, as well as the course of the adaptation, varied as a function of the strain of mouse examined. Experiment 2 was undertaken to assess the course of the adaptation evident in mice exposed to a series of different stressors, and to determine whether the strain profile was comparable to that seen after a predictable stressor regimen.

METHOD

Subjects

Experiment 2 involved 16 naive male mice of each of the strains described in Experiment 1. The subject particulars and

the animal husbandry were the same as those described in Experiment 1.

Apparatus and Procedure

In Experiment 2, mice were individually housed and acclimatized to the liquid diet as previously described. Throughout the study, water and liquid diet (as described earlier) were available ad lib from 1600 to 0800 h; food and water consumption, and body weights were measured upon removal of the liquid diet and prior to stressor application. The mice were assigned to either a Stress or Nonstress condition using the assignment procedure described in Experiment 1. Half of the mice were then exposed to a 14-day stressor regimen consisting of footshock (360 shocks of 300 uA, 2-s duration with a 9-s intertrial interval), restraint (30 min), tailshock (49 shocks of 340 μA, 2-s duration at 9-s intervals), and light exposure (112 light presentations, 4–6 footcandles, 5-s duration, 30-s intertrial interval) while the remaining mice were left undisturbed in the colony room. The sequence of stressor presentations are shown in the abscissa of Fig. 3.

The apparatus used to deliver footshock was identical to that employed in Experiment 1. Restraint stress was administered in six standard Plexiglas mouse-restraining tubes. The mouse was placed inside the tube and the gate was positioned such that movement was limited. Fiberglass tape was used to secure the tube and the gate to the surface of a table on which the restraining tube rested. The mouse's tail was secured with surgical tape to the flat surface to prevent the animal from turning around in the restraining tube. To administer tailshock, mice were placed in the restraining tubes, after which two electrical leads were attached to 3-mm strips of aluminum foil wrapped around the mid-portion and end of the mouse's tail. Shocks were delivered to the tail through the 3000-V source. Light stress was administered in four identical black Plexiglas chambers (29.2 × 8.9 × 16.5 cm) having a grid

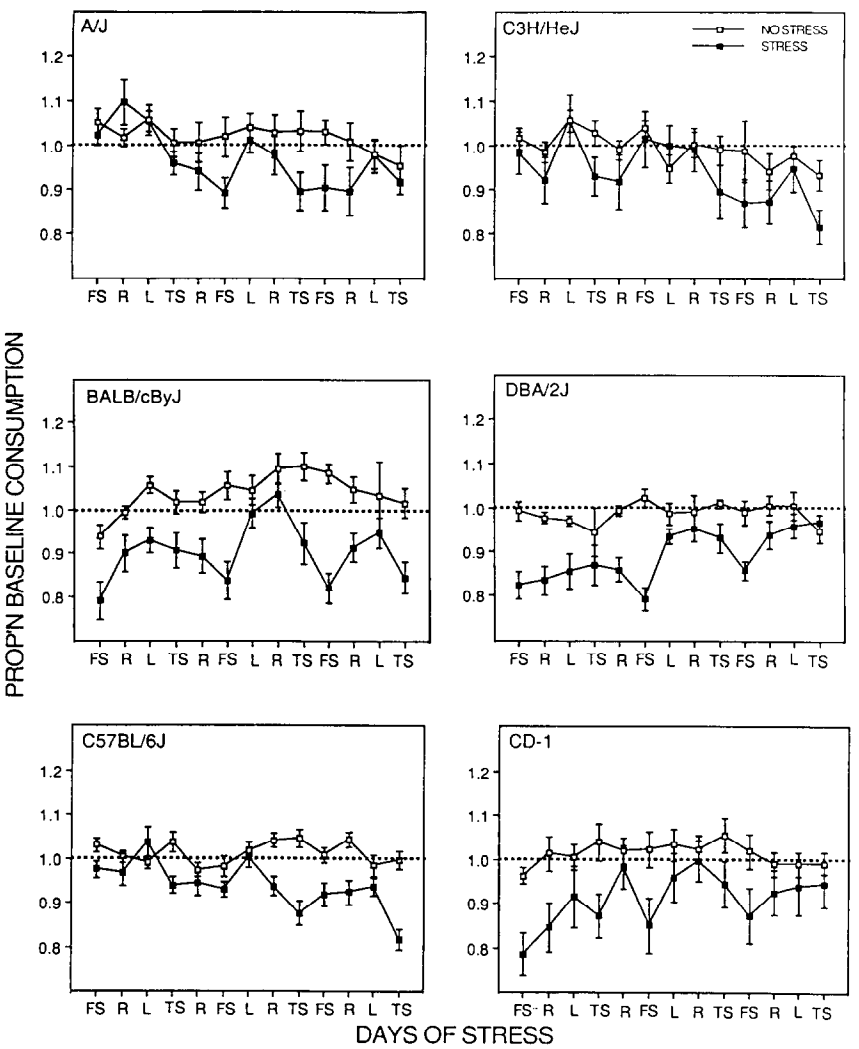

FIG. 3. Mean (±SEM) proportion of baseline consumption of a palatable liquid diet in six strains of mice following either a multiple stressor regimen or no stressor exposure (FS, footshock; R, restraint; L, light exposure; TS, tailshock).

floor and covered by red Plexiglas. Each box contained two lights (situated at one end of the box, one outside and the other below the grid floor) which could be illuminated.

RESULTS AND DISCUSSION

Consumption of the palatable diet varied as a function of the Strain × Stressor treatment × Days interaction, $F(60, 996) = 1.86$, $p < 0.01$. As shown in Fig. 3, and confirmed by Newman-Keuls multiple comparisons ($a = 0.05$), in nonstressed animals consumption of the palatable diet remained relatively stable over the course of the experiment, except in the BALB/cByJ mice where food intake unaccountably varied by as much as 10% from baseline values. The stressor treatment influenced consumption in each of the strains, but the profile of intake varied considerably across the strains. In particular, in DBA/2J and CD-1 mice, consumption was initially reduced but increased over successive days. Consumption on day 10 (a footshock day), for instance, revealed that intake exceeded that seen on earlier footshock days. In BALB/cByJ mice, consumption was initially reduced by the stressor treatment, but little adaptation was apparent over the course of the stressor regimen. A very different consumption profile was evident in the A/J, C57BL/6J, and C3H/HeJ mice. In each of these strains the effects of the stressor on food consumption became progressively more pronounced with repeated stressor application. It will be recalled that following exposure to an acute or chronic stressor in Experiment 1, consumption was unaffected in the A/J strain, while in C57BL/6J mice there was a modest decline after the initial 3 days of stress, after which consumption approached that of nonstressed animals. Clearly, the intermittent stressor of Experiment 2 effectively reduced consumption in mice that were essentially unaffected by a predictable stressor regimen, and also exacerbated the reduced consumption in strains that ordinarily exhibited recovery of consumption with repeated stressor exposure.

As shown in Fig. 4, the increase in body weight relative to baseline values ordinarily observed over the 14-day period in nonstressed mice was diminished in stressed mice. ANOVA, in fact, confirmed that the weight changes varied as a function of the Stressor treatment × Days interaction, $F(12, 996) = 32.14$, $p < 0.05$, the Strain × Days interaction, $F(60, 996) = 4.18$, $p < 0.05$, while the Strain × Stressor treatment interaction approached statistical significance, $F(5, 83) = 2.31$, $p = 0.051$. Newman-Keuls comparisons confirmed that the variations in weight change over days were more dramatic in some strains (e.g., BALB, C57, and C3H) than in others (CD-1, A/J), and that the effects of the stressor were apparent primarily during the latter part of the regimen. In addition, it appeared that the reduced weight gain associated with the stressor were significant in DBA/2J mice, approached significance in the A/J, C3H/HeJ, and C57BL/6J mice, but in the BALB/cByJ or CD-1 mice the effect of the stressor was negligible. Once again, these data clearly illustrate that there was little correspondence between the strain-specific effects of the stressors on food intake and on weight gain.

GENERAL DISCUSSION

Consistent with earlier reports (11,24), stressor exposure caused a decline in the consumption of a highly preferred diet. With repeated exposure to the stressor, adaptation developed so that consumption returned to prestress levels. Several earlier reports had indicated that exposure to a series of either unpredictable, mild (24), or relatively intense stressors (11) provoked persistent reductions in the consumption of either saccharin or sucrose. The course of the adaptation in the present investigation likewise appeared to be somewhat retarded when the stressor regimen involved the administration of a series of different aversive stimuli.

The effectiveness of an acute stressor in provoking reductions of food intake varied appreciably across strains of mice, as did the course of the adaptation in response to repeated stressor administration. In some strains the stressor initially reduced the consumption of the palatable diet, but with repeated exposure to the aversive stimulation the behavioral alterations diminished. In other strains the stressor effects were exacerbated following the initial few stressor sessions, after which adaptation began to develop. Indeed, in A/J mice, which did not display a reduction in consumption following either acute stressor application or after repeated exposure to footshock, administration of the unpredictable stressor effectively reduced consumption of the liquid diet.

It might be supposed that the strain-specific stressor effects may reflect a neophobic reaction that varied across the strains of mice. However, preliminary studies conducted in this laboratory revealed that the reduced consumption observed after stressor exposure occurred irrespective of whether the diet was a relatively novel one, or alternatively, one which animals had received since weaning. Moreover, the effects of the stressor were least marked in A/J mice, which generally is a particularly timid strain of mouse (3), and in preliminary studies exhibited the most pronounced neophobia upon first encountering the novel diet. Taken together, it appears unlikely that the strain differences observed in the present investigation are related to a neophobic reaction.

The view has been expressed that reductions in consumption of a highly preferred substance reflect the anhedonic consequences of the stressor, and that such effects might be subserved by mesolimbic DA changes provoked by the stressor (23). Consistent with such an interpretation, the strain differences in consumption of a palatable diet following an acute stressor (i.e., after a single footshock session in both Experiments 1 and 2) in the present investigation were reminiscent of the previously reported stressor-induced variations of self-stimulation responding from the prefrontal cortex (30). In particular, it was reported that footshock markedly reduced self-stimulation from the prefrontal cortex in both the BALB/cByJ and DBA/2J mice, without affecting performance in the C57BL/6J strain. Parenthetically, the latter effects could not be attributed to rate-dependent factors, since comparable basal rates of responding were evident in BALB/cByJ and C57BL/6J mice. It is important to note that the strain profile for ICSS from the nucleus accumbens could readily be differentiated from that seen in the prefrontal cortex. In particular, footshock disrupted intracranial self-stimulation (ICSS) from the nucleus accumbens in DBA/2J mice, had no effect in the C57BL/6J strain, and actually enhanced responding in BALB/cByJ mice (33). More recent as yet unpublished studies conducted in this laboratory, however, suggest that in BALB/cByJ mice a stressor could substantially reduce ICSS responding from the nucleus accumbens, but such an effect might be related to the nature and duration of the stressor regimen (8) and the extent of the training mice received (Dean & Zackarko, unpublished report).

The similarity in the strain responses for ICSS from the prefrontal cortex and the alterations of consumption of the palatable diet observed after an acute stressor raises the possibility that common mechanisms may be subserving the two. Moreover, it is conceivable that DA alterations in prefrontal

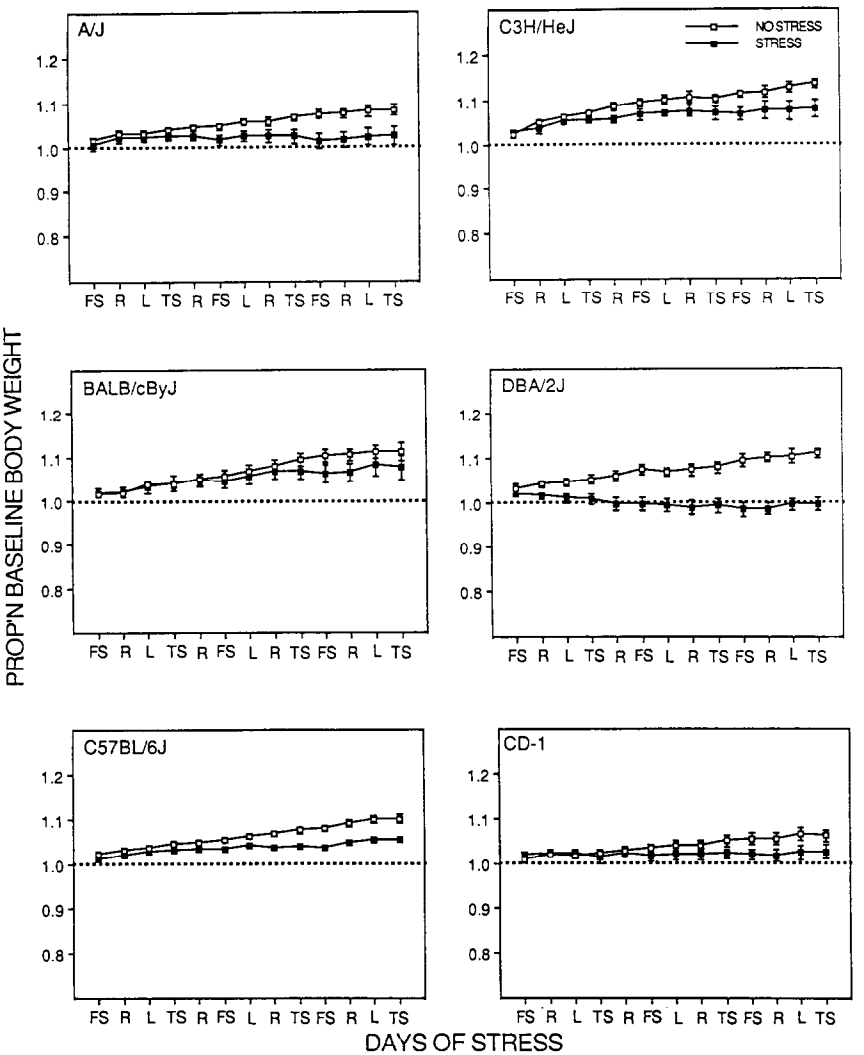

FIG. 4. Mean (±SEM) proportion baseline bodyweight in six strains of mice exposed to either a multiple stressor regimen (FS, footshock; R, restraint; L, light exposure; TS, tailshock or no stressor exposure).

cortex might play a role in this respect. Like the behavioral changes, stressor-provoked DA activation in this region, as reflected by increased L-3,4-dihydroxyphenylacetic acid (DOPAC) accumulation, was appreciably enhanced in DBA/2J mice, somewhat less in BALB/cByJ, and hardly affected in C57BL/6J (19). However, when other strains of mice are considered, the parallel between the stressor-induced neurochemical and behavioral changes, and hence the suggestion that mesolimbic DA activity subserves consumption of the palatable diet, appears to be less compelling (19). In particular, consumption of the liquid diet following acute stressor exposure was diminished in CD-1, but not in C3H/HeJ mice. Yet, DOPAC variations induced by the acute stressor were comparable in the two strains (19).

It would appear that the correspondence between strain-specific DA alterations in the prefrontal cortex were incongruent with the variations of liquid diet consumption. Yet, it may still be premature to dismiss entirely a role for mesocortical DA alterations in subserving the stressor-provoked variations of food consumption. While it is tempting, as described earlier, to ascribe a major role in this respect to DA variations in the nucleus accumbens, the pattern of DA activity seen in this region could readily be differentiated from the strain profile for consumption of the palatable diet. Specifically, acute stressor application elicited comparable DOPAC alterations across each of the strains and DA reductions were noted only in the BALB/cByJ mice (19), a profile which was entirely dissimilar from that seen with respect to liquid diet consumption in the present investigation.

One final issue with respect to the current findings warrants further attention. Typically, when alterations of food intake are considered as a symptom of depression, the defining characteristics are significant weight gain or loss, or change in appetite (2). While it might be assumed that change in appetite and weight are interdependent, the results of the present investigation, as well as earlier reports (7), suggest a considerable degree of independence between these two variables. Not unexpectedly, stressor exposure was found to influence weight

gain, and, as in the case of food intake, marked interstrain differences were evident in this respect. However, there appeared to be little correspondence between the two variables. For instance, A/J mice that did not exhibit a decline in food consumption upon exposure to a predictable stressor regimen (Experiment 1) displayed a marked retardation of weight gain which was equivalent to that seen in those strains that displayed pronounced reductions of food intake. Furthermore, as indicated earlier, the retardation of weight gain was evident throughout the testing period, despite the fact that adaptation in terms of food intake was evident in some of the strains of Experiment 1. A similar incongruence between weight change and food intake was previously shown (7,12), prompting the suggestion that the stressor treatment may have altered the animal's set point, thereby provoking the relatively persistent changes in weight (7). The fact that persistent weight changes were evident even when food intake had returned to prestress levels (as in the case of the A/J mice) suggests that the alterations in weight gain were likely attributable to factors other than food intake, such as variations in metabolic rate. Given the apparent independence of stressor-related alterations of food intake and weight change, coupled with the apparent stabilization of weight to a new lower set point following a chronic stressor, it might be appropriate to consider variations in metabolism in the analysis of the depressive symptomatology.

ACKNOWLEDGEMENTS

Supported by Grant A8945 from the Natural Sciences and Engineering Research Council of Canada to H. Anisman. The assistance of Anna Minkiewicz-Janda is gratefully acknowledged.

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