Physiology & Behavior 119 (2013) 115–129

Contents lists available at SciVerse ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Effects of chronic mild stress on rats selectively bred for behavior related to bipolar disorder and depression

Ryan Murray, Katherine A. Boss-Williams, Jay M. Weiss *

Department of Psychiatry, Emory University School of Medicine, Atlanta, GA 30306, United States

HIGHLIGHTS

- Chronic Mild Stress (CMS) reduces sucrose intake in selectively-bred rats.
- CMS causes reduction of preference for sucrose vs. water in selectively-bred rats.
- Decreases in sucrose intake and preference are not due to CMS reducing food intake.
- Overall preference for sucrose over water is reduced but persists after CMS.

ARTICLE INFO

Article history:
Received 19 December 2012
Received in revised form 28 March 2013
Accepted 24 May 2013
Available online 2 June 2013

Keywords:
Bipolar disorder
Depression
Stress
Genetic predisposition
Affective disorder
Rat model

ABSTRACT

To test the possibility that chronic mild stress (CMS) might be unreliable in producing its often-intended outcome (i.e., decreased preference for sucrose, hypothesized to represent depression-relevant anhedonia) because it is typically applied to "normal" rats, a CMS procedure was applied to rats that may possess genetic susceptibility to affective disorders, having had been selectively-bred to show behavior indicative of such disorders. These rat lines were: Hyperactive (HYPER) rats, which show characteristics of bipolar disorder, Swim-test Susceptible (SUS) and Swim-test Resistant (RES) rats, being susceptible or resistant to effects of stress in the swim test, Swim High-active (SwHi) and Swim Low-active (SwLo) rats, which innately show high or low activity in the swim test. These selectively-bred lines were compared to normal, non-selectively bred (NS) rats. During CMS, HYPER rats, both females and males, as well as RES and SwHi rats, showed reduced consumption of a palatable 2% sucrose solution, and reduced preference for sucrose (vs. water) in comparison to non-stressed rats (no CMS) of the same lines. In contrast, CMS produced no decrease in sucrose consumption or in preference for sucrose in normal NS rats, and actually a caused a slight increase in sucrose consumption and preference in male NS rats. Other measures that indicate depression – food intake and motor activity in the home cage – were also assessed. SwLo and SwHi showed greater sensitivity to having their home-cage ambulatory activity reduced by CMS than did NS rats, but no other such differences relative to NS rats were seen for these other measures; thus, changes in sucrose intake or preference could not be explained by a change in caloric intake. These results suggest that the genetic attributes of animals can influence the outcome of CMS, and that the application of CMS to normal, non-selected rats may account, at least in part, for the unreliability of CMS in decreasing consumption of palatable substances and decreasing preference for such substances.

1. Introduction

In the early 1980s Richard Katz developed the chronic unpredictable stress paradigm for use as an animal model of depression [1,2]. In the chronic unpredictable stress procedure, rats are subjected to a series of different stressors over an extended period of time (weeks to months), the stressors being varied from day to day in a random order so as to prevent habituation. In the late 1980s Paul Willner developed a modified version of Katz's chronic unpredictable stress procedure which he termed "chronic mild stress" (CMS) [3]. The main focus of the effect of CMS has been on its ability to reduce intake of a palatable sucrose or saccharine solution which both Katz and Willner believed to indicate the presence of anhedonia in rodents [2,4]. Subsequently, many investigators have utilized CMS procedures, with types and schedules of stressors used in CMS varying considerably between studies (e.g., [3,5–7]). Despite its widespread use, CMS has been the focus of considerable controversy. Perhaps the greatest concern regarding CMS has been its unreliability in producing decreases in intake of palatable solutions, particularly sucrose. While some investigators are able to get such an effect from CMS, other investigators have reported no effect (see, for example, introductory section in Ref. [8]). This concern was

* Corresponding author at: Emory University School of Medicine, Emory Briarcliff Campus, Building A, Room 510N, 1256 Briarcliff Road, N.E., Atlanta, GA 30306, USA. Tel.: +1 404 712 9771; fax: +1 404 712 9755.
E-mail address: jweis01@emory.edu (J.M. Weiss).

0031-9384/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.physbeh.2013.05.042

sufficiently widespread that Willner acknowledged it in his "10-year summary of CMS effects" [9], noting in that same publication that he himself was having difficulty reproducing his own findings after moving his laboratory and changing his animal provider.

Another significant issue has been Willner's contention that the decrease in sucrose intake produced by CMS is indicative of a loss of preference to sucrose. In the case of intake of highly palatable fluid such as a sucrose solution, to show that an animal has lost its preference for sucrose it is necessary to show not only that intake of the sucrose solution decreases but that the rat correspondingly increases its intake of water, thus reflecting "loss of preference for sucrose"; otherwise, sucrose intake might have decreased simply because CMS reduced total fluid intake. The latter would occur as follows: that stress readily decreases food intake in rodents is well established and widely known [10–13]. Insofar as sucrose is a source of calories, a stress-induced decrease in nutritive food intake could well reduce intake of sucrose without there being any influence of a change in "preference for sucrose." Additionally, even if rats are offered a non-nutritive palatable solution such as saccharine rather than sucrose, rats are prandial drinkers, meaning their fluid intake is tied to how much they eat, so a CMS-induced decrease in solid food consumption will decrease their total fluid intake. As will be discussed below, demonstrating a CMS-induced loss of preference for sucrose has proved to be quite difficult; in fact virtually all studies that have examined effects of CMS on sucrose intake find that after exposure to CMS animals still vastly prefer the sucrose solution to water (e.g., [3,14–21]).

One possibility suggested for overcoming the unreliability of the effects of CMS on the sucrose preference measure calls attention to differences between rodent strains, suggesting that some strains may be more susceptible to the effects of CMS than others, and that one should consider using susceptible rodent strains [8,22,23]. Unfortunately, a number of the studies that have examined effects of CMS in different strains, including those cited above, did not offer the animals a choice between the palatable substance and a less-palatable one (i.e., sucrose vs. water) but only assessed consumption of palatable substance or sucrose, and therefore these studies could not determine possible loss of preference for the palatable substance as opposed to simply a decrease in intake. Nielsen et al. [8] nevertheless concluded "Our results show that there is a need for rat strains in which there is a greater sensitivity for detecting stress effects."

In our review of the literature, we have found only two studies in rodents in which CMS resulted in a decrease in sucrose intake as well as a compensating increase in water intake to indicate that preference for sucrose was lost [5,6]. All other CMS studies showed only a decrease in sucrose intake (if any effect) but little or no change in water intake. Regarding the animals used in these two studies, Strekalova et al. [5] used C57BL/6N mice, which Griffiths et al. [23], in comparing effects of CMS in different strains of mice, reported this strain to show a decrease in consumption of a palatable diet when exposed to a chronic stress condition as did certain other strains, but also summarized data indicating that C57BL/6N was not particularly prone to showing depression-related behavioral or physiological changes. However, a distinguishing feature of the Streklova et al. study that may well account for the distinct loss of preference for sucrose seen in this study was that the CMS procedure was sufficiently severe that several animals died during the course of treatment; thus, severity of the stress resulting from CMS may have been quite important in producing the outcome obtained. In contrast, Pucilowski et al. [6] did use a rat line that was selectively-bred for a depression-related phenotype; they used the Flinders Sensitive rat (FSL), selectively bred for showing hypersensitivity to cholinergic agonists, a characteristic hypothesized to be present in people who are depressed [24]. Thus, Pucilowski et al. observed a CMS-induced loss of preference for a palatable sucrose solution when they used a rat that had been selectively bred for showing a depression-related characteristic.

We here continue to explore the strategy used by Pucilowski et al.; that is, we use rats selectively bred for "depression-relevant" characteristics. In the present study, rats from several lines that have been selectively bred for behavior related to affective disorders were subjected to a CMS procedure to determine whether these qualities would make them more susceptible to the effects of CMS than non-selectively bred Sprague–Dawley (NS) rats. In particular, five selectively bred lines of rats derived from Sprague–Dawley rats were studied: Hyperactive (HYPER), Swim-test Susceptible (Susceptible or SUS), Swim-test Resistant (Resistant or RES), Swim Low-active (SwLo), and Swim High-active (SwHi). The characteristics of these lines are as follows are described in the paragraph below.

HYPER animals are distinguished by the fact that they exhibit increased spontaneous nocturnal ambulatory activity compared to normal animals, as well as showing an extreme elevation of nocturnal ambulatory activity for several days (2–7 days) after being exposed to a stressor when young (2–3 months old). In contrast to this "manic-like" outburst, older male HYPER rats (10–14 months old) show profound and prolonged decreased nocturnal ambulatory activity after being exposed to a strong stressor [25], and similar-age older female rats as well as some 6 month-old male rats "cycle" between periods of hyperactivity and markedly reduced activity after exposure to a strong stressor. Based on these (and other) characteristics, it is suggested that HYPER animals may be a potential endogenous model of bipolar disorder in rats [26]. SUS rats show reduced activity in a swim test after being exposed to a stressor whereas RES rats are, as their name implies, resistant to this effect on swim test activity [27]. Thus, as indicated by swim test activity, SUS rats appear to be more susceptible to the effects of stress than NS rats when assessed in a swim test whereas RES rats appear to be more resistant to the effects of stress than NS rats in the swim test. SUS rats also can be used in a screening procedure which detects several classes of effective antidepressant drugs while not responding to drugs that often produce "false positives" in other drug screens [28]. SwLo rats show much reduced activity in the swim test (i.e., little struggle and much floating) even when they have not previously been subjected to any stressor, and, in contrast, SwHi rats show a great amount of activity (i.e., much struggling and little floating) in a swim test [29]. SwLo rats, unlike SwHi rats, also exhibit a strong "therapeutic" response in the swim test (i.e., a marked increase in struggling behavior) after chronic administration (two weeks) of activating antidepressants including tricyclics, which suggests that the SwLo rat may be an model of atypical depression [30]. For each of these selectively-bred lines, they were compared, in all experiments, to "control" rats consisting of the parent population of Sprague–Dawley rats that are bred in the normal, non-selected manner (NS) and maintained under similar conditions in our laboratory.

2. Methods

2.1. Animals and housing conditions

Prior to the start of the study, all rats were group-housed with 2–3 animals per cage in our vivarium and kept on a 12:12-h light cycle. Lights went on at 0700 h, off at 1900 h, and colony temperature was maintained between 20 and 22 °C. During the study, rats were maintained in activity-monitoring rooms where the animals were housed individually in standard size polypropylene cages (18 × 9 in.) having light sensors arrayed across the length of cage that enables recording of motor activity 24 h per day. Temperature and light cycle in the activity rooms was the same as in the vivarium. Food and water were available ad libitum, with food and water intake recorded daily. In addition, when sucrose was available in addition to water, sucrose intake was also recorded daily. Ambulatory activity was continuously recorded during the study, accumulated in 1.0-h bins throughout the day, and separated into dark-phase and light-phase activity for analysis.

2.2. Experimental design

Prior to any CMS procedures being given, rats were placed into an activity-monitoring room as described above and the study began with a seven day baseline period. During this baseline period, activity and consumption were measured. Sucrose was provided in addition to water for three days starting on the third day of the baseline period and ending on the fifth day; this established a baseline measure for sucrose intake. The sucrose solution given during baseline and also during the subsequent CMS period was a 2% sucrose solution that rats consume readily. Following the baseline period, the rats were divided into two groups: stressed and non-stressed (i.e., CMS-treated vs. non-CMS-treated). Animals of each rat line were allocated to these two groups based on the measurements made during the baseline period, with the groups matched on the following variables (in order from greatest to least priority): sucrose intake, body weight, dark phase motor activity, light phase motor activity, food intake, and water intake. In some cases, not all variables could be matched so that the two groups were equated, although sucrose intake, body weight, and dark phase motor activity of the groups were always closely matched.

After the baseline period was over, rats in the stressed group were subjected to the CMS procedure which lasted 27 days; the non-stress group simply remained in their home cages. It should be noted that to avoid possible transmission of stress to adjacent animals via pheromones, the CMS-treated rats and the non-CMS-treated rats were housed in separate activity-recording rooms during the CMS phase of the study. The CMS procedure used in this study consisted of eight different stressors (see Table 1) randomly repeated three times each during the course of the experiment. There were also three days during the CMS phase on which rats were subjected to no stressors.

Whenever the 2% sucrose solution was given to rats, it was given for three consecutive days. This was done three times during the experiment: during the baseline period (days 3–5) as described above, in the middle of the CMS procedure (days 17–19), and on the last three days of the CMS procedure (days 32–34). Regarding sucrose presentation during the CMS phase, it should be noted that an exception to the randomness of the CMS schedule described above was that a three-day sequence of restraint, foot shock, and no-stress (in that order) was always used during each sucrose exposure period during CMS; this was done so that sucrose intake during the two periods of exposure during CMS could be compared with each other without possible differences due to different stressors being used at each time. Only in the case of the first sucrose administration period during CMS to female rats was this particular order of stressors not used. Additionally, it should be noted food deprivation as a component of CMS has been said to be sufficient to cause a decrease in sucrose intake, hypothesized to be due to decreased caloric intake as a result of decreased metabolism [17,18,31]. However, it has also been found that increasing the time between food deprivation and presentation of sucrose to over 24 h is sufficient to eliminate a decrease in sucrose intake during CMS, presumably because of elimination of the effects of food deprivation [18,32]. Because a decrease in sucrose intake could have resulted from proximity of sucrose presentation to food deprivation, any food deprivation stressor was always administered at least 96 h before the start of a sucrose presentation period, and thus the effects of stress (CMS) on sucrose intake and/or preference for sucrose observed in this study cannot be attributed to the use of food deprivation during CMS.

Table 1
Stressors used in Chronic Mild Stress (CMS) regimen.

Stressor	Abbreviation	Description
Restraint	Res	Rats were individually restrained for 2 h
Food deprivation	FDep	Food was removed from cages for 24 h (water available ad libitum).
Overnight illumination	NiLi	Lights were left on overnight thus extending the rats light phase to 24 h.
White noise	WN	Rats were subjected to 1 h of 95 dB white noise.
Foot shock	Shk	Rats placed on a grid floor and foot shocks delivered for 1 h session at 1.0 to 1.5 mA.
Bedding switch	BedS	Rats were placed in other rats cages for 48 h. Wet bedding was applied the day after.
Wet bedding	WetB	The bedding of each cage was soaked with 450 ± 5 ml of water and changed after 24 h.
Forced swim	Swim	Rats were placed in a shallow tank of water at 78 °F for 15 min.
None	None	No stressors administered

2.3. Experiments

2.3.1. Experiment 1

This experiment studied female HYPER rats. Rats used in the study included 41st generation female HYPER rats (n = 12) and female non-selected rats (n = 12). Rats of each line were divided equally into a stressed and non-stressed group so that each group consisted of n = 6 HYPER and n = 6 non-selected rats. At the start of the experiment, female HYPER and non-selected rats were 4–6 months old. As stated above, stressed and non-stressed groups were matched as described above.

2.3.2. Experiment 2

This experiment studied male HYPER rats. Rats used in the study included 43rd generation male HYPER rats (n = 12) and male non-selected rats (n = 12). As for female HYPER rats, each line was divided into a stressed and non-stressed group of n = 6 HYPER and n = 6 non-selected rats. At the start of the experiment, male HYPER and non-selected rats were 6–8 months old. Stressed and non-stressed groups were matched as described above.

2.3.3. Experiment 3

This experiment studied male SUS and male RES rats. Rats used in the study included 44th generation male SUS rats (n = 12), 44th generation male RES rats (n = 12), and male non-selected rats (n = 12), 36 being the maximum number of rats our activity rooms could accommodate. For this study, groups were divided into stressed and non-stressed groups at a 2:1 ratio of stressed-to-unstressed animals. Thus, the stressed group consisted of n = 8 SUS rats, n = 8 RES rats, and n = 8 non-selected rats (for a total of n = 24 rats), while the non-stressed group consisted of n = 4 SUS rats, n = 4 RES rats, and n = 4 non-selected rats (for a total of n = 12 rats). At the start of the experiment SUS, RES, and non-selected rats were 6–7 months of age. Stressed and non-stressed groups were matched as described above.

2.3.4. Experiment 4

This experiment studied male SwHi and SwLo rats. Rats used in the study included 40th generation male SwHi rats (n = 12), 40th generation male SwLo rats (n = 12), and male non-selected rats. As with the previous experiment, groups were divided into stressed and non-stressed groups at a 2:1 ratio of stressed-to-unstressed animals. Thus, the stressed groups consisted of n = 8 SwHi rats, n = 8 SwLo rats, and n = 8 non-selected rats (for a total of n = 24 rats), and the non-stressed groups consisted of n = 4 SwHi rats, n = 4 SwLo rats, and n = 4 non-selected rats (for a total of n = 12 rats). At the start of the experiment the SwHi, SwLo, and non-selected rats were 3.5–4.5 months old. Stressed and non-stressed groups were matched as described above.

One SwLo rat from the stressed group died in the middle of the experiment and its data was subsequently removed from all statistical analyses.

2.4. Statistical analysis

All variables were analyzed using a three factor analysis of covariance (rat line × stress/no stress × day) with repeated measures across the day factor, the covariate being the mean for that measure across the baseline days. In experiments with three rat lines, in addition to the overall analysis comparing all three rat lines, separate analyses of the same type were carried out comparing two rat lines to each other. Finally, within each rat line the stressed and non-stressed groups were compared to each other using a two factor analysis of covariance (stress/no stress × day) with repeated measures across the day factor, the covariate again being obtained in the same manner as described above.

Some special notations are as follows: in the analysis of dark phase motor activity, data obtained on those days when overnight illumination and wet bedding stressors were used as stressors were left out of the analyses (six days total) because these manipulations markedly decreased or increased ambulatory activity. In the analyses of food intake, data obtained on those days when food deprivation stressor was administered (three days) were left out of the analyses since food intake was completely absent on such days. In addition, the days on which rats were given sucrose were left out of the analyses of food intake because the availability of sucrose decreased food intake; this was done during the baseline period (omitted from determining covariate) and during the CMS phase.

Sucrose intake was analyzed in two different ways. First, an analysis was done that included all days on which sucrose was available during the CMS phase. As previously described, a three factor, repeated measures analysis of covariance was done, using mean sucrose intake during baseline (pre-CMS, days 3–5) as the covariate for each rat. In addition, a second analysis was done that examined sucrose intake on the first day of each of the two sucrose exposure periods during the CMS phase. Again, data were analyzed by a three factor repeated measures analysis of covariance, using the first day of sucrose intake during baseline (day 3) as the covariate. The reason for the second analysis that considered sucrose intake only on the first day of each sucrose exposure period is that this time period (i.e., 24 h sucrose intake) is often used in other CMS studies and is reported in the literature, so that comparison of the results obtained here to other studies can be made. Still other CMS studies have used consumption over a 1–2 h sucrose exposure, but such a short exposure period has been reported to be less accurate than a 24 h exposure period [19,32,33]. Thus, we analyze sucrose intake across the two 3-day exposures during the CMS phase that we utilized, and also sucrose intake in the first 24 h period of each of these exposures.

Sucrose preference – i.e., the extent to which sucrose was preferred over water – was also analyzed. The more water animals ingest when sucrose is also available, the less the animal prefers sucrose. To quantify water intake relative to sucrose intake, the ratio of water intake to total fluid intake (WI:TFI) was computed for each day that both sucrose and water were available. The higher this value is, the more water is consumed relative to total fluid intake, and therefore the less sucrose is preferred. This indicator of sucrose preference was then analyzed statistically in the same manner as sucrose intake described above.

A small number of aberrant animals ($n = 3$) were not included in the sucrose analyses. In contrast to rats that typically consume over 90% of their fluid intake as sucrose on any day when the sucrose solution as well as water is available, these three rats consumed less than 50% of their fluid intake as sucrose on at least one day during the baseline period and overall showed a greatly reduced sucrose preference relative to other rats; insofar as they did not show a typical preference for sucrose to begin with, these animals were omitted from analyses of sucrose consumption. In Experiment 1, one female non-selected rat consumed less than 50% of its total fluid intake as sucrose on two days of baseline, and overall intake of the sucrose solution across the three days of baseline was 50.6% of its total fluid intake compared to all other rats in this study whose intake of the sucrose solution averaged 94.6% of total fluid intake, with a standard deviation (SD) around this mean of 4.4%; thus, intake of the sucrose solution by the aberrant rat was 9.9 SDs lower than the mean of the other animals in the experiment. In Experiment 4, two male SUS rats showed an even more pronounced lack of preference for sucrose. Across the three days of baseline, these two rats average intake of sucrose was 28.5% and 12.8% respectively of their total fluid intake compared to all other rats in this experiment whose intake of sucrose averaged 97.0% of their total fluid intake, with a SD around this mean of 1.8%; thus, sucrose intake of these two rats was 39.2 and 48.1 SDs lower than the mean of the other animals in the experiment. In summary, these three rats showed essentially no preference for sucrose as do typical rats, and their tendency to consume the sucrose solution as opposed to water differed from other rats at well beyond the .00001 level.

All experimental methods in the study were approved by the Emory University Institutional Animal Care and Use Committee (IACUC #214-2009).

3. Results

3.1. Sucrose intake

3.1.1. HYPER rats

Fig. 1 (top) shows the sucrose intake of stressed and non-stressed female Non-selected (NS) and HYPER rats. As can be seen in the Figure, compared to the amount of sucrose ingested on the initial presentations before the CMS phase (shown at left of dotted lines), sucrose intake tended to increase with successive three-day presentations that occurred during the CMS phase, particularly on the first day of each of these presentations. Regarding statistical analysis, when sucrose intake on all days during the CMS (stress) phase of the study was analyzed by a three factor (rat line × stress condition × day) repeated measures analysis of covariance (mean sucrose intake of each animal prior to CMS phase as the covariate), a significant difference between the rat lines was found [$F(1, 18) = 12.958$, $p = .002$] thereby indicating that sucrose intake of female HYPER rats was significantly lower than sucrose intake of female NS rats during the CMS phase. Most importantly, a significant rat line × stress condition interaction was found [$F(1, 18) = 7.590$, $p = .013$], thereby indicating stress vs. non-stress affected sucrose intake in HYPER females differently from NS females. Fig. 1 shows that whereas stress tended to increase sucrose consumption in NS females, stress had the opposite effect of decreasing sucrose consumption in HYPER females. Comparison of the stress vs. non-stress conditions within each of the two rat lines by similar repeated measures analysis of covariance revealed that in HYPER females sucrose intake of stressed rats was indeed significantly lower than that of non-stressed rats [$F(1, 9) = 12.184$, $p = .007$]. In NS females, however, the tendency of stress to increase sucrose intake compared with non-stress did not reach statistical significance [$F(1, 8) = 2.428$, $p = .158$].

When only the first day of each exposure period was analyzed similarly, a significant difference between rat lines was found [$F(1, 18) = 6.909$, $p = .017$], but the interaction of rat line × stress/no stress did not reach significance [$F(1, 18) = 2.681$, $p = .119$]. When the stress vs. non-stress conditions were compared within each rat line, stressed HYPER females showed significantly lower sucrose intake than non-stressed HYPER females [$F(1, 9) = 7.383$, $p = .024$], while there was no significant difference between stressed and non-stressed NS females [$F(1, 8) = 0.394$, $p = .548$].

Fig. 1 (bottom) shows the sucrose intake of stressed and non-stressed male NS and HYPER rats. As can be seen in this figure, males rats showed similar effects as were seen in females; that is, compared to the amount of sucrose ingested on the initial presentations before the CMS phase (shown at left of dotted lines), sucrose intake also tended to increase with successive three-day presentations that occurred during the CMS phase, particularly on the first day of each of these presentations. Regarding statistical analysis, when sucrose intake on all days during the CMS

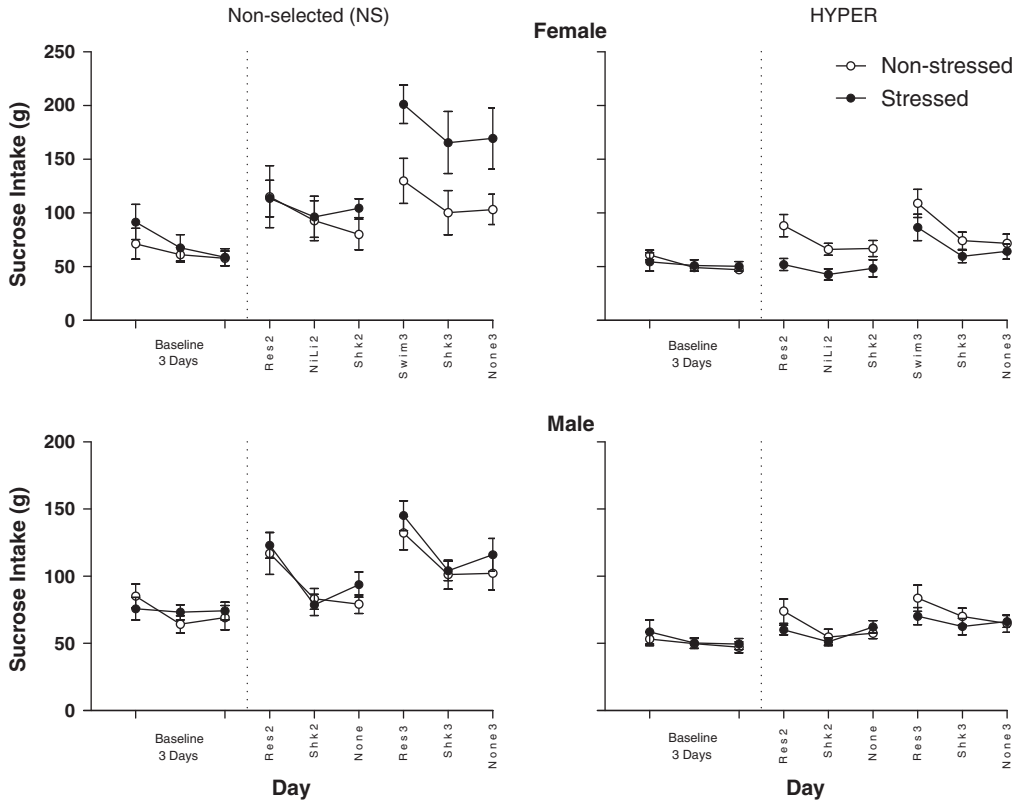

Fig. 1. Sucrose intake (ml of 2.0% sucrose solution ingested) on each day of the three 3-day segments that sucrose solution was available to female and male Non-selected (normal, NS) and HYPER rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). "Stressed" animals received the stressor conditions while "Non-stressed" animals did not. For stressed animals, the left of dotted line shows daily intake in the segment prior to stressors being applied (Baseline), and to the right of dotted line shows intake during the two segments when stressors were applied. Mean and standard error for each day is shown. Results for female rats are shown in upper graphs (one experiment) and for male rats are shown in lower graphs (another experiment). X-axis labels indicate which stressor was implemented on each day; for explanation of abbreviations see Table 1.

(stress) phase of the study was analyzed as described above for the females rats, a significant difference between the rat lines was found [$F(1, 19) = 13.229$, $p = .002$] thereby indicating that sucrose intake of male HYPER rats during the CMS phase was significantly lower than sucrose intake of male NS rats. The interaction of rat line × stress/no stress was significant [$F(1, 19) = 4.625$, $p = .045$], which indicated that stress vs. non-stress affected sucrose intake in HYPER males differently from NS males. Fig. 1 shows that, as was seen in female HYPER rats, stress tended to increase sucrose consumption in NS males while having the opposite effect of decreasing sucrose consumption in HYPER males. Comparison of the stress vs. non-stress conditions within each of the two rat lines by similar repeated measures analysis of covariance revealed that the lower sucrose intake of stressed HYPER males compared with non-stressed HYPER males approached significance [$F(1, 9) = 3.916$, $p = .079$] while the difference between stressed and non-stressed NS males was not significant [$F(1, 9) = 1.147$, $p = .312$].

When only the first day of each exposure period was analyzed similarly, the significant difference between rat lines was found [$F(1, 19) = 20.015$, $p = .001$], and a significant interaction of rat line × stress/no stress was also evident [$F(1, 19) = 8.127$, $p = .010$]. This significant interaction was supported when the stress vs. non-stress conditions were compared within each rat line. Stressed HYPER males showed significantly lower sucrose intake than non-stressed HYPER males [$F(1, 9) = 5.236$, $p = .048$], while the tendency of stressed NS males to show higher sucrose intake than non-stressed NS males approached significance [$F(1, 9) = 3.528$, $p = .093$].

3.1.2. SUS and RES rats

Fig. 2 (top) shows the sucrose intake of both stressed and non-stressed male NS, SUS and RES rats. As was seen in the results described above, sucrose intake tended to increase during with successive presentations that occurred during the CMS (stress) phase relative to the initial ingestion of sucrose before the CMS (stress) phase, Regarding statistical analysis, when sucrose intake on all days during the CMS (stress) phase of the study was analyzed by a three factor (rat line × stress condition × day) repeated measures analysis of covariance (mean sucrose intake of each animal prior to CMS phase as the covariate), a significant difference between rat lines was found [$F(2, 27) = 11.637$, $p = .001$]. The data shown in Fig. 3 indicates that this resulted from the sucrose intake of RES rats being lower than that of NS and SUS rats. Similar analyses comparing pairs of rat lines confirmed this, revealing that sucrose intake of NS and SUS rats during the CMS phase did not differ significantly [$F(1, 17) = 1.969$, $p = .179$] whereas the RES rats showed significantly lower sucrose intake than NS rats [$F(1, 19) = 9.389$, $p = .006$] and SUS rats [$F(1, 17) = 33.364$, $p = .000$]. The interaction of rat line × stress/no stress was not significant [$F(2, 27) = .322$, $p = .728$], which indicated that stress did not affect different rat lines differently. This result was supported by comparison of stress vs. non-stress within each rat line, which revealed no significant differences within the SUS, RES, or NS rat lines [$F(1, 7) = .000$, $p = .998$; $F(1, 9) = .211$, $p = .657$; and $F(1, 9) = .656$, $p = .439$ respectively].

When only the first day of each exposure period was analyzed similarly, the significant difference between rat lines remained [$F(2, 27) = 18.715$, $p = .000$]. Further analyses comparing pairs of rat lines revealed that SUS rats showed the highest sucrose intake, their intake being significantly higher compared to NS rats [$F(1, 17) = 5.152$, $p = .037$] and RES rats [$F(1, 17) = 52.272$, $p = .000$]. RES rats showed the lowest sucrose intake, not only being lower than SUS rats but significantly lower than NS rats as well [$F(1, 19) = 14.804$, $p = .001$]. The interaction of rat line × stress/no stress was not significant in the ANOVA

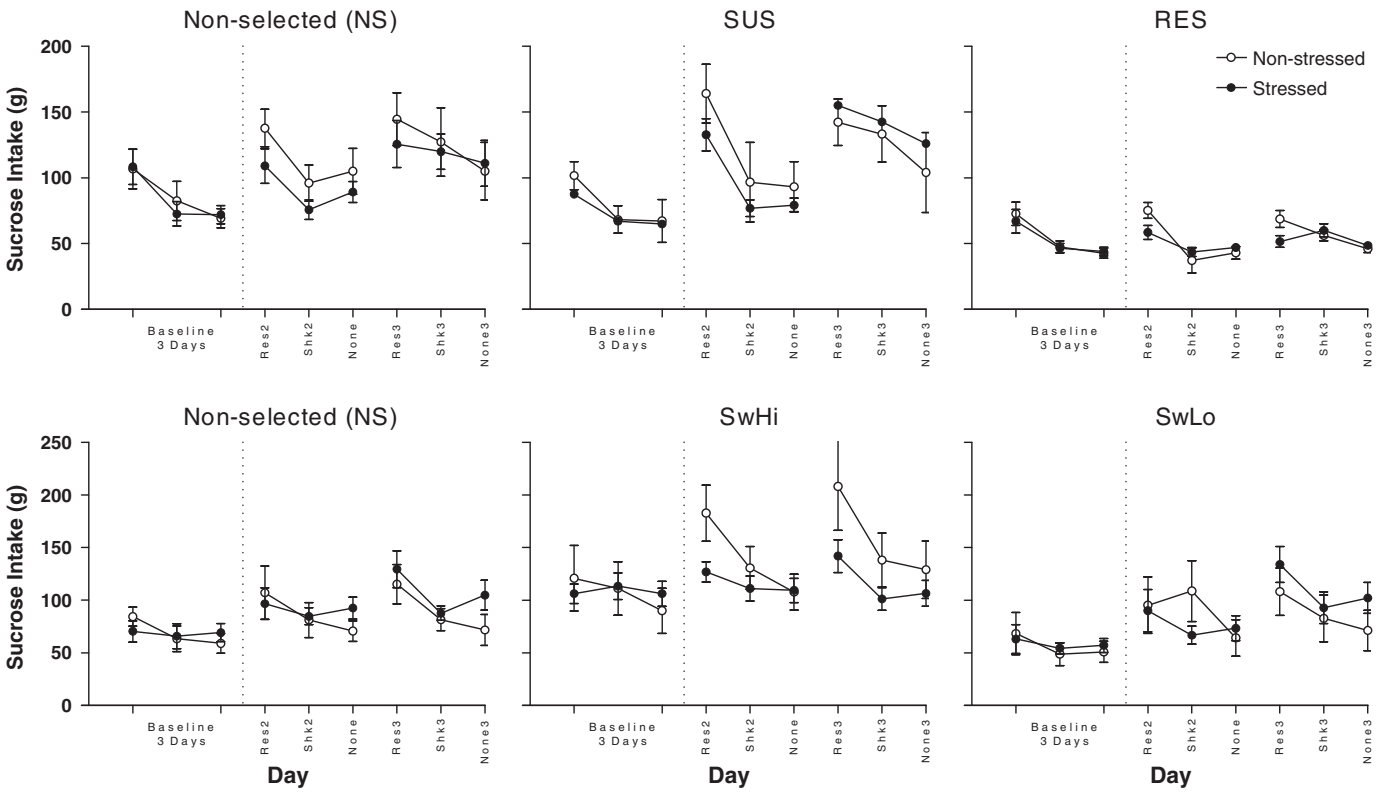

Fig. 2. Sucrose intake (ml of 2.0% sucrose solution ingested) on each day of the three 3-day segments that sucrose solution was available to male Non-selected (normal, NS) vs. Susceptible (SUS), Resistant (RES), Swim-High active (SwHi), or Swim-Low active (SwLo) rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). Results for NS, SUS and RES rats are shown in upper graphs (one experiment) and for NS, SwHi and SwLo rats are shown in lower graphs (another experiment). All other aspects of graphs are the same as in Fig. 1.

that included all three rat lines [$F(2, 27) = .593$, $p = .560$], nor was this interaction significant in any ANOVA where pairs of rat lines were compared. However, when intake of stressed vs. non-stressed rats were compared within each rat line, SUS rats did not show a significant difference [$F(1, 7) = .087$, $p = .776$], but for RES and NS rats stressed rats tended to show lower sucrose intake than non-stressed rats [$F(1, 9) = 4.639$, $p = .060$, and $F(1, 9) = 3.718$, $p = .086$ respectively].

3.1.3. SwHi and SwLo rats

Fig. 2 (bottom) shows the sucrose intake of both stressed and non-stressed male NS, SwHi, and SwLo rats. As was seen previously, sucrose intake tended to increase during with successive presentations that occurred during the CMS (stress) phase. Regarding statistical analysis, when sucrose intake on all days during the CMS (stress) phase of the study was analyzed by a three factor (rat line × stress condition × day) repeated measures analysis of covariance (mean sucrose intake of each animal prior to CMS phase as the covariate), there was no significant effect of rat line [$F(2,28) = 0.409$, $p = .668$] but the interaction of rat line × stress/no stress was significant [$F(2,28) = 3.649$, $p = .039$], thereby indicating that stress vs. non-stress affected sucrose intake differently in different rat lines. Fig. 2 shows that this interaction occurred because stress decreased the sucrose intake of SwHi rats relative to the heightened intake of non-stressed SwHi, but SwLo and NS rats showed little difference between stressed and non-stressed. Analyses comparing pairs of rat lines revealed a significant rat line × stress/no stress interaction when SwHi and NS rats were compared [$F(1, 19) = 6.221$, $p = .022$], and that this interaction approached significance when SwHi and SwLo were compared [$F(1, 18) = 3.564$, $p = .075$]. This interaction was not significant when SwLo and NS lines were compared [$F(1, 18) = .634$, $p = .436$]. These results were supported by comparison of stressed and non-stressed rats within each line, which showed that stressed SwHi rats consumed less sucrose than non-stressed SwHi rats [$F(1, 9) = 6.161$, $p = .035$], while there was no such difference between stressed and non-stressed rats of the SwLo and NS lines [$F(1, 8) = .152$, $p = .707$, and $F(1, 9) = .828$, $p = .387$, respectively].

When only the first day of each exposure period was analyzed similarly, the interaction of rat line × stress/no stress was also significant [$F(2, 28) = 3.518$, $p = .043$]. Further analyses comparing pairs of rat lines revealed a significant interaction of rat line × stress/no stress between SwHi and NS rats [$F(1, 19) = 5.526$, $p = .030$] and SwHi and SwLo rats [$F(1, 18) = 4.719$, $p = .043$], thereby indicating that stress reduced the intake of sucrose intake in SwHi rats but did not do so in NS and SwLo rats. Comparison of stressed and non-stressed rats within each line showed that stressed SwHi rats had significantly lower sucrose intake than non-stressed SwHi rats [$F(1, 9) = 6.773$, $p = .029$] whereas stressed and non-stressed of NS and SwLo rats did not differ [$F(1, 9) = .712$, $p = .421$, and $F(1, 8) = .155$, $p = .704$ respectively].

3.2. Preference for sucrose (vs. water)

Affinity for sucrose can be measured not only by the amount of sucrose consumed but also by the relative amount of water consumed; the more water consumed when sucrose is available, the less the preference for sucrose, and vice versa. Therefore, one can determine how strong the preference for sucrose is by calculating the ratio of water consumed to the total fluid ingested (water + sucrose) on each of the days that sucrose was offered. As stated above, the higher the ratio of water consumed to total intake, the lower the preference for sucrose, and vice versa. This measure we refer to below as preference for water.

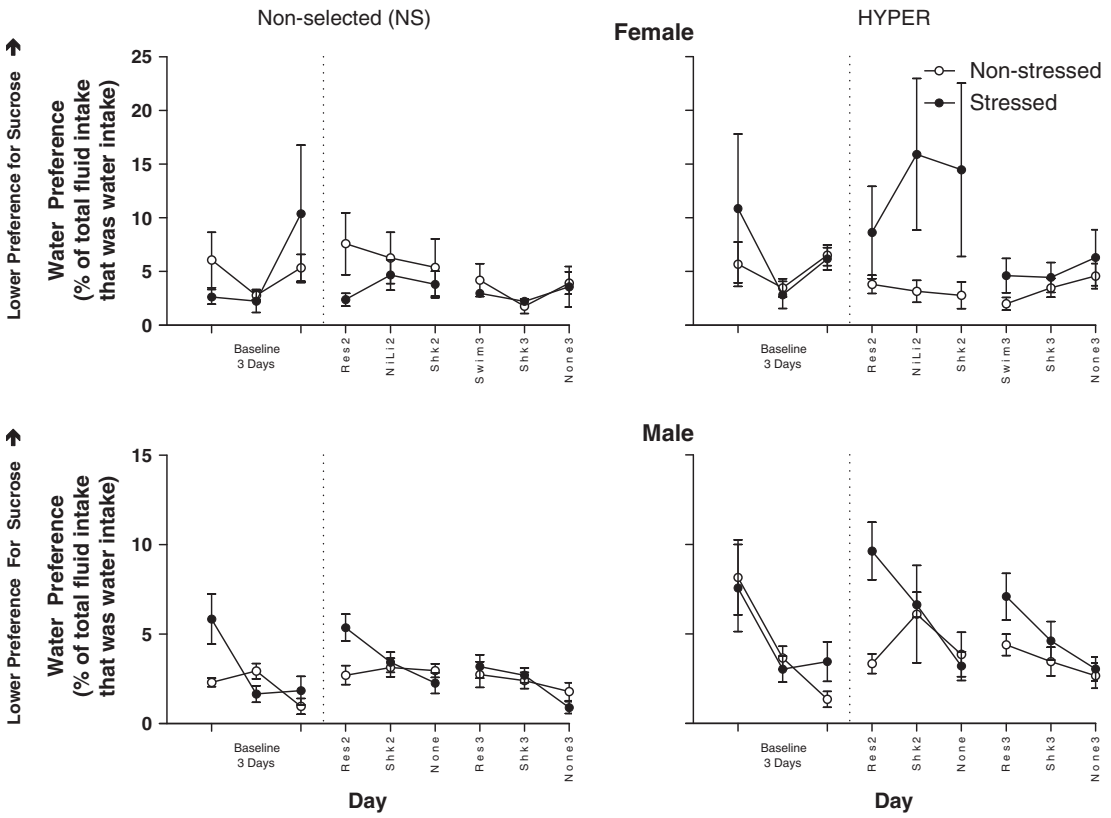

Fig. 3. Preference for water (i.e., percent of total fluid intake that was water) on each day of the three 3-day segments that 2% sucrose solution also was available to female and male Non-selected (normal, NS) and HYPER rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS); higher preference for water indicates lower preference for sucrose solution. Results for female rats are shown in upper graphs (one experiment) and for male rats are shown in lower graphs (another experiment). All other aspects of graphs are the same as in Fig. 1.

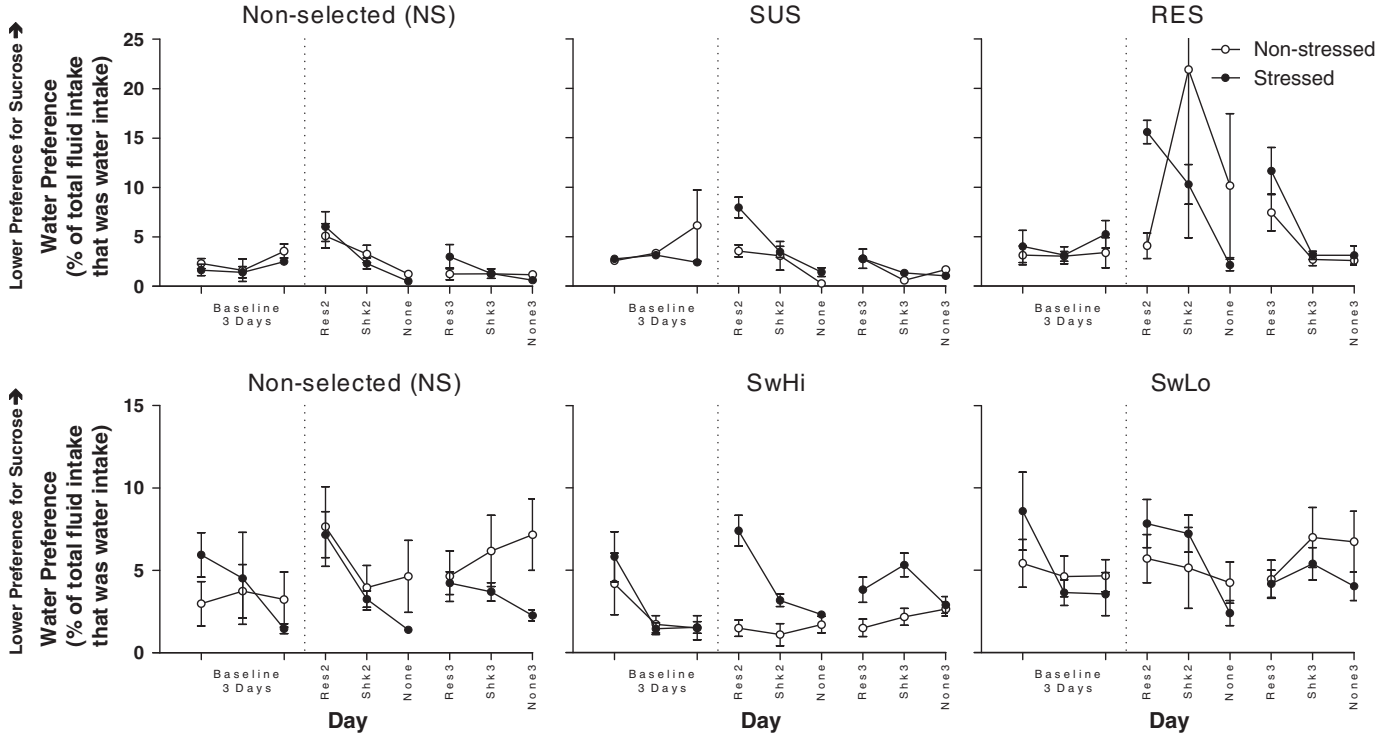

Fig. 4. Preference for water (i.e., percent of total fluid intake that was water) on each day of the three 3-day segments that 2% sucrose solution also was available to male Non-selected (normal, NS), Susceptible (SUS), Resistant (RES), Swim-High active (SwHi), or Swim-Low active (SwLo) rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS); higher preference for water indicates lower preference for sucrose solution. Results for NS, SUS and RES rats are shown in upper graphs (one experiment) and for NS, SwHi and SwLo rats are shown in lower graphs (another experiment). All other aspects of graphs are the same as in Fig. 1.

3.2.1. HYPER rats

Fig. 3 (top) shows preference for water of both stressed and non-stressed female NS and HYPER rats. When all days on which rats were offered sucrose as well as water were analyzed by a three factor repeated measures analysis of covariance as described for sucrose intake in the previous section, a significant interaction of rat line × stress/no stress was found [$F(1, 18) = 5.439$, $p = .032$], thereby indicating that preference for water was affected differently by stress in female HYPER and NS rats. Fig. 3 shows that this occurred because stress increased preference for water (i.e., decreased preference for sucrose) in HYPER females but not in NS females. This significant interaction was supported by comparison of stress and non-stress conditions within each rat line, which revealed that stressed HYPER females showed significantly higher preference for water (and therefore lower preference for sucrose) than non-stressed HYPER females [$F(1, 9) = 16.078$, $p = .003$] whereas stressed and non-stressed NS females did not show a significant difference in preference for water [$F(1, 8) = .859$, $p = .381$].

When only the first day of each exposure period was analyzed similarly, the interaction of rat line × stress/no stress approached significance [$F(1, 18) = 3.344$, $p = .084$] thereby indicating that the preference for water tended to be affected differently by stress in female HYPER and NS rats. However, comparison of stress and non-stress within rat lines revealed that while stress tended to increase preference for water in HYPER females, the difference was not significant [$F(1, 9) = 2.895$, $p = .123$], nor was the tendency for stress the decrease preference for water in NS females [$F(1, 8) = .952$, $p = .358$].

Fig. 3 (bottom) shows preference for water of both stressed and non-stressed male NS and HYPER rats. When all days in which rats were offered sucrose as well as water were analyzed by a three factor repeated measures analysis of covariance as described previously, a significant difference between rat lines was found [$F(1, 19) = 8.497$, $p = .009$], thereby indicating HYPER males showed significantly higher preference for water (and therefore lower preference for sucrose) compared with NS males. The interaction of rat line × stress/no stress approached significance [$F(1, 19) = 4.004$, $p = .060$], thereby indicating that preference for water tended to be affected differently by stress in male NS and HYPER rats. Fig. 3 shows that this occurred because stress increased the preference for water (i.e., decreased the preference for sucrose) in HYPER males more so than in NS males. This interaction effect was supported by comparison of stress and non-stress conditions within each rat line, which revealed that a higher preference for water (and therefore lower preference for sucrose) in stressed HYPER males in comparison to non-stressed HYPER males approached significance [$F(1, 9) = 4.234$, $p = .070$], whereas there was no indication of a difference in preference for water between stressed and non-stressed NS males [$F(1, 9) = .001$, $p = .973$].

When only the first day of each exposure period was analyzed similarly, a significant difference between rat lines was also found [$F(1, 19) = 11.998$, $p = .003$], thereby indicating that HYPER males showed higher preference for water overall than did NS males. More importantly, the interaction of rat line × stress/no stress was significant [$F(1, 19) = 5.405$, $p = .031$] thereby indicating that preference for water was affected differently by stress in male HYPER and NS rats. Fig. 3 shows that this occurred because stress increased preference for water much more so in HYPER males than in NS males. The interaction effect was supported by comparison of stress vs. non-stress with each rat line, which revealed that stressed HYPER males showed significantly higher preference for water than did non-stressed HYPER males [$F(1, 9) = 14.965$, $p = .004$], whereas preference for water was not significantly different when stressed and non-stressed NS males were compared [$F(1, 9) = 3.106$, $p = .112$].

3.2.2. SUS and RES rats

Fig. 4 (top) shows the preference for water of stressed and non-stressed male NS, SUS, and RES rats. When all days in which rats were offered sucrose as well as water were analyzed by a three factor repeated measures analysis of covariance as described in the Methods section, a significant difference between rat lines was found [$F(2, 27) = 8.970$, $p = .001$], which indicated that different rat lines showed significantly different preference for water. Further analyses comparing pairs of rat lines revealed that preference for water did not differ when SUS and NS rats were compared [$F(1, 17) = .296$, $p = .593$] whereas RES rats showed significantly higher preference for water (and therefore lower preference for sucrose) when compared with either NS or SUS rats [$F(1, 19) = 7.293$, $p = .014$ and $F(1, 17) = 9.343$, $p = .007$ respectively]. However, the interaction of rat line × stress/no stress was not significant [$F(2, 27) = .552$, $p = .599$], which indicated that stress did not affect water preference differently in the rat lines.

When only the first day of each exposure period was analyzed similarly, the significant difference between rat lines remained [$F(2, 27) = 10.226$, $p = .000$]. Further analyses comparing pairs of rat lines revealed that preference for water did not differ when SUS and NS were compared [$F(1, 17) = .002$, $p = .963$], but RES rats showed significantly higher preference for water when compared with either NS or SUS rats [$F(1, 19) = 12.176$, $p = .002$, and $F(1, 17) = 12.856$, $p = .002$ respectively]. The interaction of rat line × stress/no stress approached significance [$F(2,27) = 3.229$, $p = .052$], thereby indicating that preference for water tended to be affected differently by stress in different rat lines. Further analyses comparing pairs of rat lines revealed that the interaction of rat line × stress/no stress did not differ when SUS and NS rats were compared [$F(1, 17) = .020$, $p = .890$], while this interaction approached significance when RES rats were compared with either NS or SUS rats [$F(1, 19) = 4.167$, $p = .055$, and $F(1, 17) = 3.737$, $p = .070$ respectively]. These results were supported by comparisons of stressed and non-stressed rats within each rat line, which revealed that preference for water (and therefore lower preference for sucrose) was distinctly higher in stressed RES rats than in non-stressed RES rats [$F(1, 9) = 9.655$, $p = .013$] while this difference did not reach significance in either SUS or NS rats [$F(1, 7) = 4.292$, $p = .077$ and $F(1, 9) = 1.110$, $p = .320$ respectively].

3.2.3. SwHi and SwLo rats

Fig. 4 (bottom) shows the preference for water of both stressed and non-stressed male SwHi, SwLo, and NS rats. When all days in which rats were offered sucrose as well as water were analyzed by a three factor repeated measures analysis of covariance as described previously, the rat line × stress/no stress interaction was significant [$F(2, 28) = 6.106$, $p = .006$]. When pairs of rat lines were compared in the same manner, significant rat line × stress/no stress interactions were found comparing SwHi and NS rats [$F(1, 19) = 14.610$, $p = .001$], and SwHi and SwLo rats [$F(1, 18) = 4.956$, $p = .039$], thereby indicating that stress increased preference for water (i.e., decreased preference for sucrose) more so in SwHi rats than in NS or SUS rats. The interaction of rat line × stress/no stress between SwLo and NS rats was not significant [$F(1, 18) = 1.430$, $p = .247$], which indicated that stress did not affect SwLo and NS rats differently. These results were supported by the evidence that stressed SwHi rats showed significantly higher preference for water (and therefore lower preference for sucrose) than did non-stressed SwHi rats [$F(1, 9) = 12.629$, $p = .006$]. In contrast, preference for water did not differ for stressed and non-stressed SwLo rats [$F(1, 8) = .326$, $p = .583$] while in NS rats, stressed rats tended to show lower preference for water (i.e., higher preference for sucrose) compared to non-stressed NS rats [$F(1, 9) = 4.687$, $p = .059$.], opposite to the effect of stress seen in SwHi rats.

When only the first day of each exposure period was analyzed similarly, a difference between rat lines was found that approached significance [$F(2, 28) = 2.766$, $p = .080$] as did the interaction of rat line × stress/no stress [$F(2, 28) = 2.699$, $p = .085$]. Further analyses comparing pairs of rat lines revealed that SwHi rats showed

significantly lower preference for water compared to NS rats [$F(1, 19) = 5.567$, $p = .029$], while the difference between SwHi and SwLo rats did not reach significance [$F(1, 18) = 2.842$, $p = .109$] nor was there a difference when NS and SwLo rats were compared [$F(1, 18) = .474$, $p = .500$]. Importantly, the interaction of rat line × stress/no stress was significant when SwHi and NS rats were compared [$F(1, 19) = 5.307$, $p = .033$]. This interaction did not reach significance when SwHi and SwLo rats were compared [$F(1, 18) = 3.095$, $p = .096$] or when SwLo and NS rats were compared [$F(1, 18) = .303$, $p = .589$]. These results were supported by the evidence from comparison of stress and non-stress rats within each rat line. In SwHi rats, stress caused an increase in water preference (i.e., reduced preference for sucrose) relative to non-stressed rats [$F(1, 9) = 11.694$, $p = .008$], whereas stress produce no such difference in SwLo or NS rats [$F(1, 8) = .053$, $p = .824$, and $F(1, 9) = .383$, $p = .551$ respectively].

3.3. Food intake

3.3.1. HYPER rats

Fig. 5 (top) shows the food intake of both stressed and non-stressed female NS and HYPER rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between stress groups [$F(1, 19) = 10.566$, $p = .004$], thereby indicating that stressed females overall showed significantly lower food intake than did non-stressed females. More importantly, the interaction of rat line × stress/no stress was not significant [$F(1, 19) = .389$, $p = .540$], indicating that stress did not affect female NS and HYPER rats differently. Comparison of stress vs. non-stress within rat lines revealed that stressed NS females showed significantly lower food intake than did non-stressed NS females [$F(1, 9) = 5.445$, $p = .044$] while this difference did not reach significance in the HYPER females [$F(1, 9) = 3.035$, $p = .115$].

Fig. 5 (bottom) shows the food intake of both stressed and non-stressed male NS and HYPER rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between rat lines [$F(1, 19) = 10.085$, $p = .005$], thereby indicating that HYPER males showed significantly lower food intake than did NS males during the CMS phase. As with the females, there was a significant difference attributable to stress [$F(1, 19) = 7.395$, $p = .014$], thereby indicating that stressed males overall showed significantly lower food intake than did non-stressed males. The interaction of rat line × stress/no stress was not significant [$F(1, 19) = .036, .852$], indicating that stress did not affect food intake of HYPER and NS males differently. Comparison of stress vs. non-stress within rat lines, however, revealed that stressed HYPER males showed significantly lower food intake than did non-stressed HYPER males [$F(1, 9) = 7.579$, $p = .022$], and that this difference, though in the same direction, did not reach significance for NS males [$F(1, 9) = 1.905$, $p = .201$].

3.3.2. SUS and RES rats

Fig. 6 (top) shows the food intake of both stressed and non-stressed male NS, SUS and RES rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between rat lines [$F(2, 29) = 4.194$, $p = .025$], thereby indicating that different rat lines showed significantly different food intake during the CMS phase. Further analyses comparing pairs of rat lines revealed that RES rats showed significantly lower food intake than NS and SUS rats [$F(1, 19) = 8.291$, $p = .010$, and $F(1, 19) = 4.063$, $p = .058$ respectively]. SUS and NS rats did not show significantly different food intake [$F(1, 19) = 1.919$, $p = .182$].

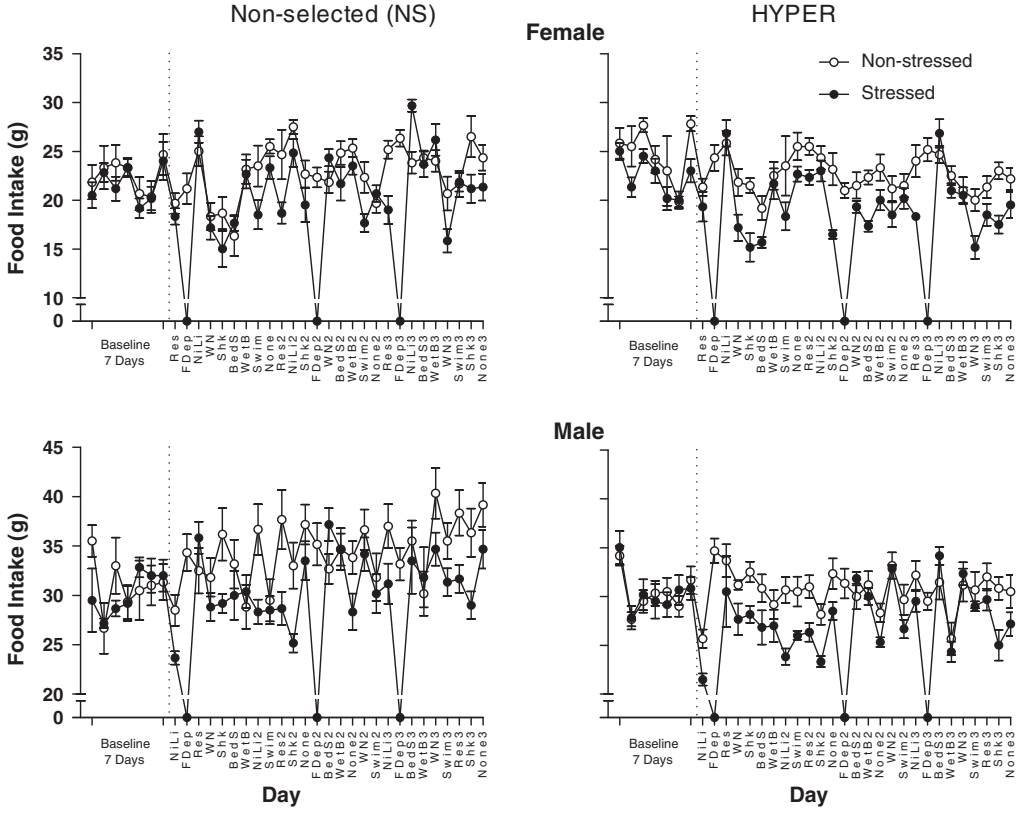

Fig. 5. Food intake on each day (grams of food eaten) for female and male Non-selected (normal, NS) and HYPER rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). Results for female rats are shown in upper graphs (one experiment) and for male rats are shown in lower graphs (another experiment). Short lines just above the x axis denote days on which sucrose administration during CMS took place. All other aspects of graphs are the same as in Fig. 1.

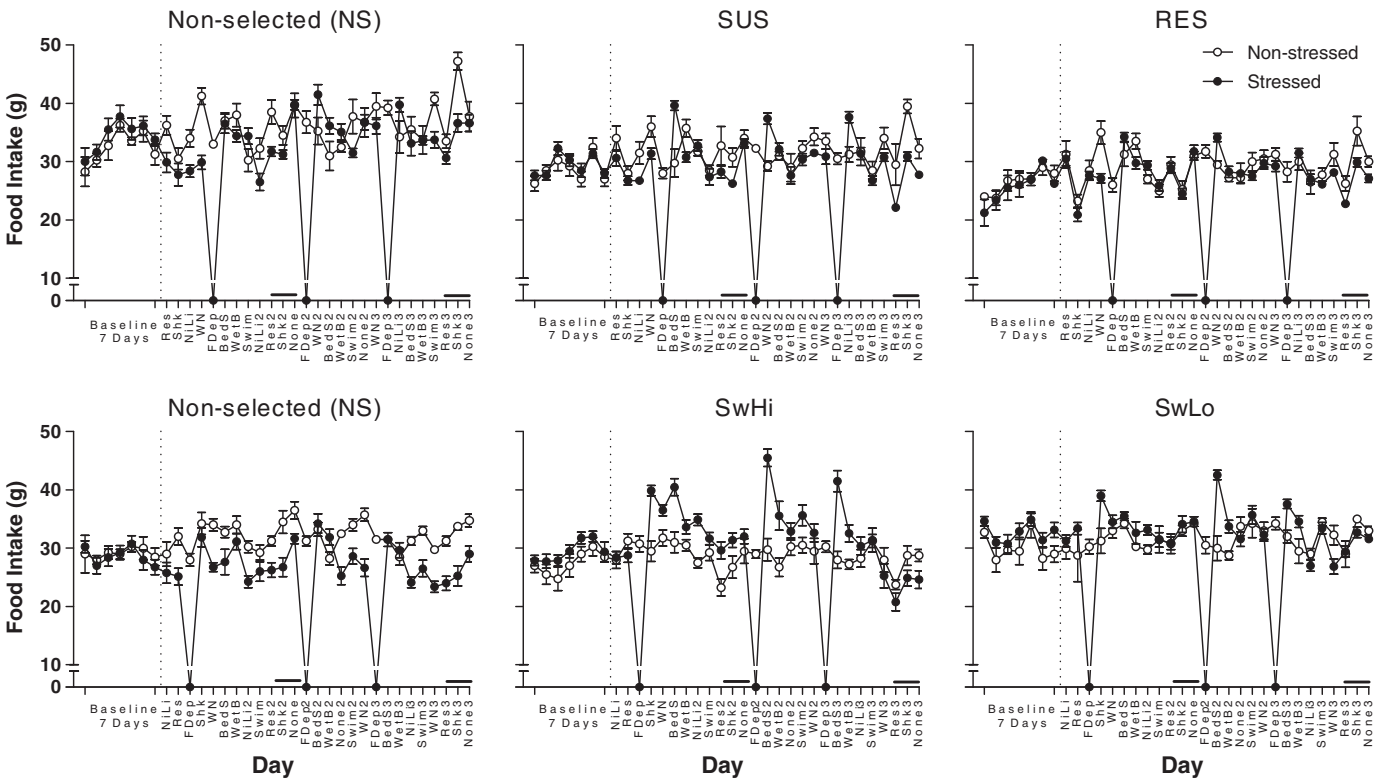

Fig. 6. Food intake on each day (grams of food eaten) for male Non-selected (normal, NS), Susceptible (SUS), Resistant (RES), Swim-High active (SwHi), or Swim-Low active (SwLo) rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). Results for NS, SUS and RES rats are shown in upper graphs (one experiment) and for NS, SwHi and SwLo rats are shown in lower graphs (another experiment). Short lines just above the x axis denote days on which sucrose administration during CMS took place. All other aspects of graphs are the same as in Fig. 1.

The interaction of rat line × stress/no stress was not significant, [$F(2, 29) = .993$, $p = .383$], thereby indicating that there was not a significant difference in how stress affected food intake of the different rat lines. However, comparison of stress vs. non-stress within each rat line revealed that stressed NS rats showed significantly lower food intake than non-stressed NS rats [$F(1, 9) = 9.158$, $p = .014$], and stressed SUS rats tended to show lower food intake than non-stressed SUS rats [$F(1, 9) = 3.409$, $p = .098$]. Compared to these two rat lines, food intake of stressed and non-stressed RES rats did not differ significantly [$F(1, 9) = 1.032$, $p = .336$].

3.3.3. SwHi and SwLo rats

Fig. 6 (bottom) shows the food intake of both stressed and non-stressed male NS, SwHi and SwLo rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant interaction of rat line × stress/no stress [$F(2, 28) = 7.353$, $p = .003$], thereby indicating that stress affected the food intake of the rat lines differently. Further analyses showed that SwHi rats, which often showed increased food intake in response to CMS, responded to CMS differently from both NS and SwLo rats. Analyses comparing pairs of rat lines revealed a significant interaction of rat line × stress/no stress when SwHi rats were compared to either NS rats or SUS rats [$F(1, 19) = 11.568$, $p = .003$, and $F(1, 18) = 4.657$, $p = .045$ respectively]. When SwLo and NS rats were compared, the interaction of rat line × stress/no stress also approached significance [$F(1, 18) = 4.376$, $p = .051$], thereby indicating that the stress-induced decrease in food intake of NS rats differed from the lesser effect of stress on food intake in SwLo rats. When stress vs. non-stress was compared within each rat line, SwHi rats actually showed a tendency toward stress-induced elevation of food intake [$F(1, 9) = 2.902$, $p = .123$], SwLo rats showed no significant difference in stress vs. non-stress food intake [$F(1, 8) = .201$, $p = .666$], and NS rats showed significantly lower food intake of stressed rats relative to non-stressed rats [$F(1, 9) = 7.898$, $p = .020$].

3.4. Dark phase motor activity

3.4.1. HYPER rats

Fig. 7 (top) shows the dark phase motor activity of both stressed and non-stressed female NS and HYPER rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between rat lines [$F(1, 19) = 16.871$, $p = .001$], indicating that female HYPER rats showed significantly higher ambulatory activity during the dark phase than did female NS rats. Insofar as HYPER rats show elevated ambulatory activity compared to normal rats, this was an expected finding. No other effect comparing female HYPER and NS rats was significant.

Fig. 7 (bottom) shows the dark phase motor activity of both stressed and non-stressed male HYPER and NS rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between rat lines [$F(1, 19) = 5.622$, $p = .028$], indicating that, as was seen in the females, male HYPER rats showed, as expected, significantly higher ambulatory activity during the dark phase than did male NS rats. There was a near-significant overall effect of stress [$F(1, 19) = 4.264$, $p = .053$], indicating a general tendency for dark phase activity to be lower in stressed animals compared with non-stressed animals. When stress vs. non-stress was compared within each rat line, this difference did not reach significance within the HYPER rats [$F(1, 9) = 2.483$, $p = .150$], but it did approach significance within the NS rats [$F(1, 9) = 4.043$, $p = .075$]. Not surprisingly, the interaction of rat line × stress/no stress was not significant [$F(1, 19) = .488$, $p = .493$].

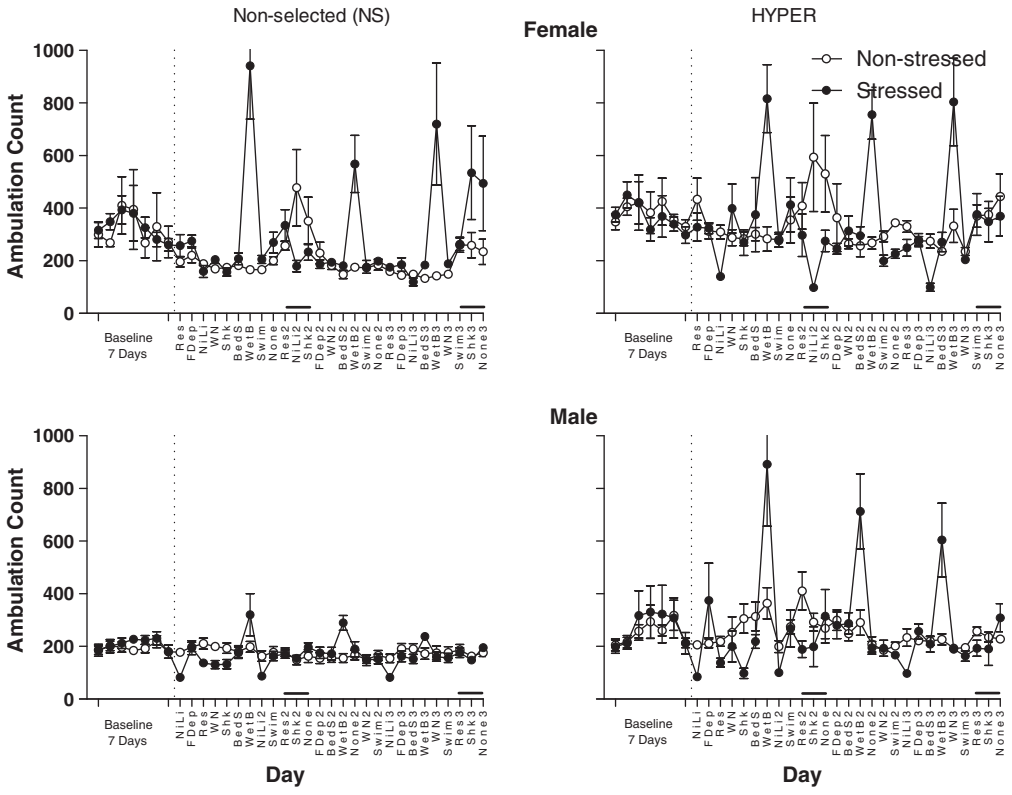

Fig. 7. Ambulatory activity during the 12-h dark portion of the day (activity counts per hour are shown) on each day for female and male Non-selected (normal, NS) and HYPER rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). Results for female rats are shown in upper graphs (one experiment) and for male rats are shown in lower graphs (another experiment). Short lines just above the x axis denote days on which sucrose administration during CMS took place. All other aspects of graphs are the same as in Fig. 1.

3.4.2. SUS and RES rats

Fig. 8 (top) shows the dark phase motor activity of both stressed and non-stressed male NS, SUS and RES rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant difference between rat lines, $F(2, 29) = 11.655$, $p = .000$, which indicated that the rats lines differed significantly in amount of ambulation during the dark phase. Further analyses comparing pairs of rat lines revealed that the dark phase ambulatory activity of RES rats was significantly lower than either NS or SUS rats [$F(1, 19) = 8.017$, $p = .011$, and $F(1, 19) = 21.653$, $p = .000$ respectively], while SUS rats conversely showed the highest dark phase ambulation, being significantly higher not only than RES rats but NS rats as well [$F(1, 19) = 4.451$, $p = .048$]. The ANOVA containing all groups showed a significant overall difference between stress and non-stress [$F(1, 29) = 13.187$, $p = .001$], and, more importantly, a significant interaction of rat line × stress/no stress [$F(2, 29) = 3.908$, $p = .031$], the latter indicating that stress/no-stress affected dark phase ambulatory activity differently in the different rat lines. Further analyses comparing pairs of rat lines revealed that the interaction of rat line × stress/no stress was significant when SUS and RES lines were compared [$F(1, 19) = 6.871$, $p = .017$], thus indicating that stress reduced the higher dark phase ambulation of SUS rats while having little effect on the lower ambulation of RES rats. This interaction did not reach significance when SUS rats were compared to NS rats [$F(1, 19) = 1.555$, $p = .228$] or when RES were compared to NS [$F(1, 19) = 2.635$, $p = .121$]. These results were supported by the evidence that stressed SUS rats showed significantly lower dark phase motor activity than did non-stressed SUS rats [$F(1, 9) = 11.067$, $p = .009$], while comparison of stress vs. no stress within RES rats showed no significant difference in dark phase activity [$F(1, 9) = .020$, $p = .889$]. Within NS rats, stress produced a near-significant decrease in dark phase activity compared with non-stress [$F(1, 9) = 4.844$, $p = .055$].

3.4.3. SwHi and SwLo rats

Fig. 8 (bottom) shows the dark phase motor activity of both stressed and non-stressed male NS, SwHi and SwLo rats. The three factor repeated measures analysis of covariance as described in the Methods section yielded a significant overall difference between stress vs. non-stress [$F(1, 28) = 36.245$, $p = .000$], and, more importantly, the interaction of rat line × stress/no stress was significant [$F(2,28) = 5.066$, $p = .013$], the latter indicating that stress/no stress affected dark phase ambulatory activity differently in the different rat lines. Further analyses comparing pairs of rat lines revealed that the interaction of rat line × stress/no stress between SwHi and NS rats was significant [$F(1, 19) = 9.809$, $p = .005$], while this interaction approached significance when SwLo and NS rats were compared [$F(1, 18) = 3.347$, $p = .084$]; these effects showed that stress decreased dark phase ambulation more so in both SwHi and SwLo rats than in the NS rats. The interaction of rat line × stress/no stress was not significant when SwHi and SwLo rats were compared [$F(1, 18) = 1.910$, $p = .184$]. These results were supported by comparison of stress vs. no stress within each rat line, which revealed that both SwHi and SwLo rats showed significantly lower dark phase ambulation than non-stressed SwHi and SwLo rats [$F(1, 9) = 32.712$, $p = .000$, and $F(1, 8) = 12.396$, $p = .008$ respectively], while the difference between stressed and non-stressed NS rats was not significant [$F(1, 9) = 1.069$, $p = .328$].

3.5. Effects of CMS: relationship between measures

To assess whether the effect of CMS on different rat lines was similar across the various measures taken, a correlation matrix showing

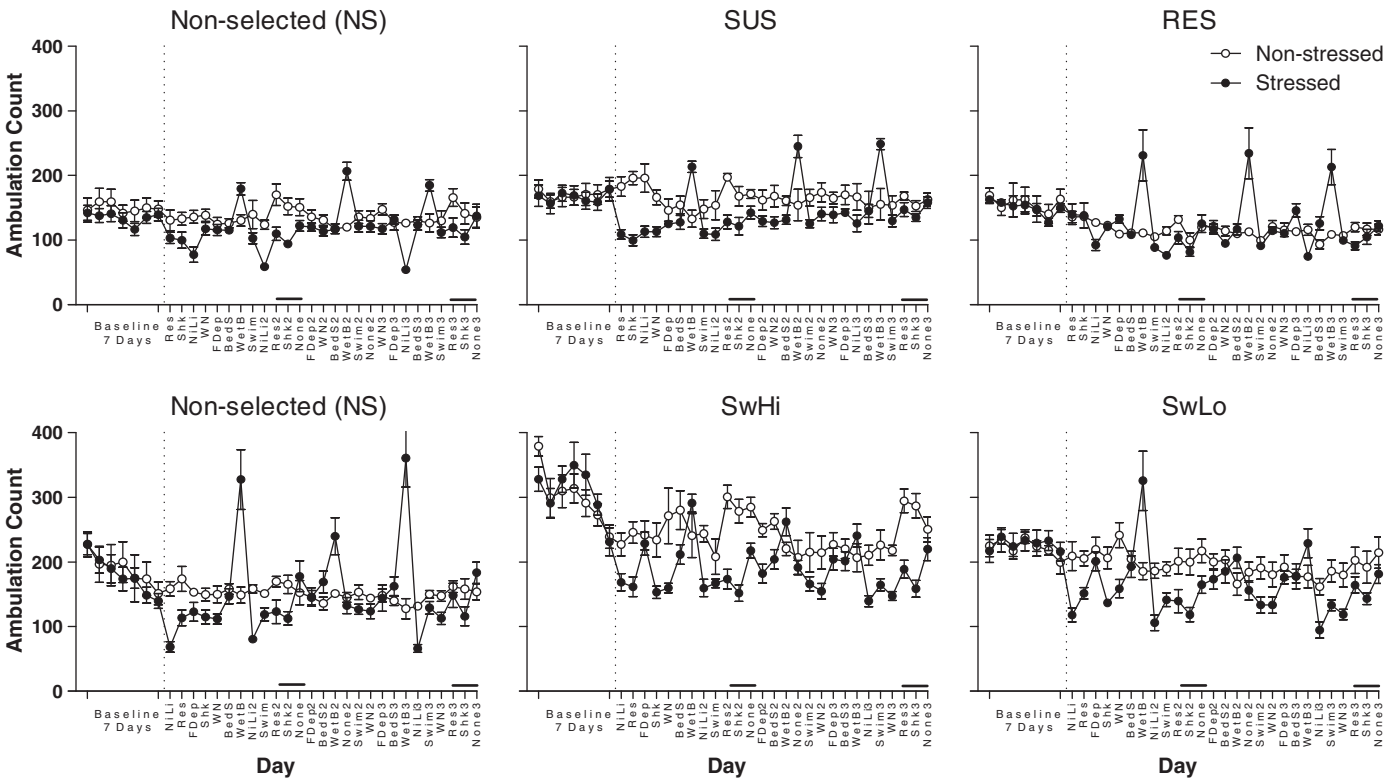

Fig. 8. Ambulatory activity during the 12-h dark portion of the day (activity counts per hour are shown) on each day for male Non-selected (normal, NS), Susceptible (SUS), Resistant (RES), Swim-High active (SwHi), or Swim-Low active (SwLo) rats prior to and during daily application of various stressful conditions constituting "chronic mild stress" (CMS). Results for NS, SUS and RES rats are shown in upper graphs (one experiment) and for NS, SwHi and SwLo rats are shown in lower graphs (another experiment). Short lines just above the x axis denote days on which sucrose administration during CMS took place. All other aspects of graphs are the same as in Fig. 1.

the relationship between effects of CMS on the different measures was calculated. To do this required reducing the data for each rat line on any given measure into a single number, so that a correlation coefficient then could be computed. This was done by first averaging the scores for each animal on a measure (i.e., amount of sucrose ingested, percent of fluid intake that was water, etc.) across all the days of the CMS procedure to obtain a single number for each animal, and then the mean of the subjects in that condition was computed. To express the effects of CMS for each line of rats on that measure, a ratio was computed by dividing the mean for the stressed (CMS-exposed) rats by the mean for non-stressed rats of that line; a ratio below 1.00 indicated that CMS tended to reduce the measure whereas a ratio above 1.00 indicated that CMS tended to increase the measure. Using this ratio as the single number expressing the effect of stress for each rat line on each measure, correlations between measures across the rat lines were computed, and the intercorrelation matrix is shown in Table 2.

Inspection of this matrix reveals that measures relating to sucrose ingestion (i.e., sucrose intake and preference for water [inverse of preference for sucrose]) were highly correlated with one another (i.e., similar effects of stress on these measures) across the different rat lines (as would be expected, correlations between measures of sucrose intake and preference for water were negative, thereby indicating that in rat lines where CMS decreased sucrose intake, it increased preference for water [i.e., decreased preference for sucrose]). As described earlier, CMS decreased sucrose intake and increased preference for water (i.e., decreased preference for sucrose) in certain selectively-bred rat lines, and this effect of CMS was seen consistently in all measures taken. Interestingly, effects of CMS on food intake did not correlate significantly with effects on sucrose intake or preference for sucrose, again confirming that CMS-induced changes in measures of sucrose intake did not relate to any changes in food intake. Finally, CMS-induced changes in motor activity (dark phase) correlated somewhat with changes in sucrose produced by CMS; for one measure, the correlation was significant while for three others the correlation was not. The correlation between changes in food intake and motor activity was moderate, but in an unexpected direction — the correlation was negative, indicating that CM-induced decreases in motor activity tended to be associated with smaller decreases in food intake produced by CMS or CMS-induced increases in food intake across the different rat lines. However, this correlation did not reach significance.

4. Discussion

In the study reported here, we examined the effects of CMS on measures of behavior thought to be indicative of depression in the rat, principally consumption of a palatable sucrose solution, as well as amount of food intake and ambulatory activity during the dark portion of the day (when the rat is normally most active) during the time that the CMS procedure was being administered. The selectively-bred rat lines indeed differed in how they reacted to CMS, and particularly when compared to NS rats. We describe first perhaps the principal results of these studies, which are effects on sucrose consumption and preference for sucrose. Changes in sucrose consumption have been the focus of CMS studies since the CMS technique was first described by Katz [2] and subsequently pursued by Willner [3]; both authors suggest that decreased sucrose intake and/or decreased preference for sucrose indicates a loss of ability to appreciate rewarding stimuli, considered by some to be the cardinal symptom of depression [34].

Although no rat line we tested ever exhibited an actual loss of preference for sucrose when stressed (insofar as a loss of preference for sucrose would be indicated by consumption of sucrose at 50% or

Table 2
Correlation matrix of variables studied.

	Sucrose intake (all days)	Sucrose intake (first days only)	Preference for water (all days)	Preference for water (first days only)	Food intake	Dark phase motor activity
Sucrose intake (all days)	–	**0.94***	**−0.83***	**−0.84***	−0.16	**0.72***
Sucrose intake (first days only)		–	**−0.75***	**−0.90***	−0.12	0.53
Preference for water (all days)			–	**0.72***	0.08	−0.46
Preference for water (first days only)				–	0.50	−0.59
Food intake					–	−0.51
Dark phase motor activity						–

Values represent the Pearson correlation coefficients for the relevant measure of the row versus the relevant measure of the column. Significant correlations ($p < .05$) are shown in boldface with superscript star.

less of total fluid intake), nonetheless certain rat lines exhibited decreased sucrose consumption and/or decreased preference for sucrose as a result of CMS. To begin, non-selected (NS) rats, or "normal" Sprague–Dawley rats, did not show a consistent tendency to decrease sucrose consumption or preference for sucrose as a result of being exposed to CMS, which is in accord with (a) the oft-reported failure of CMS to produce this outcome in normal rats, and (b) the unreliability of CMS in such rats (e.g., [8,35,9] with attached commentaries). The reason for this study, in fact, was to determine if our selectively-bred lines of rats, which may contain genetically-based determinants that predispose animals to depression, might show decreased sucrose intake or reduced preference for sucrose in response to CMS more readily than do NS rats. In contrast, when compared to what was seen in NS rats, HYPER rats, both females and males, showed decreased sucrose consumption and reduced preference for sucrose (i.e., higher intake of water when sucrose was available) as a result of being exposed to CMS. The CMS-induced decrease in both sucrose consumption and preference for sucrose in HYPER rats was largest in the first 24 h of each of the two periods of sucrose presentation during CMS. In SwHi and SwLo rats (males), SwHi rats also showed reduced sucrose consumption and reduced preference for sucrose during CMS, whereas SwLo males, like NS rats, manifested no effect of CMS on sucrose intake or preference. In RES and SUS rats, RES rats, which overall consumed less sucrose than SUS or NS rats, also showed a decrease in both sucrose intake and preference for sucrose in response to CMS, and this effect was again most evident the first 24 h. of each sucrose presentation during CMS. In summary, rats of selectively-bred lines tested in this study – namely, HYPER, SwHi, and RES rats – showed, when exposed to the CMS procedure, significantly reduced sucrose consumption and reduced preference for sucrose (vs. water) in comparison to how normal (NS) Sprague–Dawley rats responded to CMS.

Interestingly, the effects of CMS on food intake were quite different from what was seen for sucrose consumption, with the findings for food intake indicating that decreases in sucrose consumption described above did not derive from any general decrease in energy metabolism. This is an important because it has been proposed that the reduction in preference for sucrose caused by CMS can be due to a reduction in the caloric intake of rats [18,31]. In NS rats, CMS significantly decreased their food intake in three out of four experiments, only falling short of causing a significant decrease in the study that contrasted NS rats with HYPER males. Thus, while food intake was decreased by the stress of CMS in NS rats, this did not translate into decreased sucrose consumption or decreased preference for sucrose in these rats. Amongst the selectively-bred rats, CMS significantly reduced food intake only in HYPER males (and not in HYPER females). In SwHi rats, which showed decreased sucrose consumption and decreased preference for sucrose as a result of CMS, the CMS procedure actually tended to *increase* their food intake. In RES rats, which also showed decreases in sucrose consumption and preference with CMS, there was no evidence that of any CMS-induced decrease in their food intake. That effects of CMS on food intake were unrelated to effects of CMS on sucrose intake or preference for sucrose (i.e., preference for water) was also evident from the correlational analysis of measures shown in Table 2.

With regard to effects on ambulatory activity during the dark phase of the day (when rats are most active), this measure assesses whether CMS might have caused a depression of motor activity. CMS decreased dark phase ambulation in some of the selectively-bred rats. In no experiment did CMS significantly decrease dark phase ambulation of NS rats, although in two of the three experiments with male NS rats the difference between stress and non-stressed NS rats approached significance. Not unexpectedly, HYPER rats, both males and females, showed considerably higher dark phase activity in general than any other line of rats; moreover, exposure to CMS did not reduce this elevated activity. Regarding the other rat lines, SUS rats had the highest level of dark phase activity, and, when exposed to CMS, this high level of activity was markedly and significantly lowered by CMS. In contrast, their counterpart line, RES rats, had the lowest level of dark phase ambulatory activity, and CMS did not decrease this further. In SwHi and SwLo rats, CMS significantly decreased dark phase ambulation in both lines, and both lines differed in this respect from NS rats that were not similarly affected. In summary, "CMS-induced depression of motor activity in the home cage" was found in SUS, SwHi, and SwLo rats, but not in the other lines.

To summarize, CMS reduced sucrose consumption and preference for sucrose in certain selectively-bred rat lines, while not having this effect in NS rats. Reduced sucrose intake and preference was seen in HYPER (male and female), SwHi, and RES rats. In contrast, CMS reduced food intake in NS rats and, in the selectively-bred lines, only in HYPER males. Depression of ambulatory activity in the home cage as a result of CMS was seen in SUS, SwHi, and SwLo rats. A summary of the effects of CMS on the various measures assessed in this study is shown in Table 3.

Consumption of sucrose has been linked to activity of dopamine (DA) in the mesocortical DA system, particularly in the shell of the nucleus accumbens (NAcc). Previously, we measured in all of the selectively-bred rats studied here the concentration of dopamine (DA) in NAcc, as well as concentration of the dopaminergic metabolite homovanillic acid (HVA) which is indicative of dopamine release in NAcc [26]. With regard to how DA release in NAcc affects sucrose consumption, other investigators have shown that DA release increases in the shell of NAcc when sucrose is consumed, that infusion of a drug into NAcc that blocks DA reuptake and therefore potentiates DA activity will increase sucrose intake, and that administration of a DA antagonist decreases sucrose consumption [36,37]. Other studies have shown that DA release in shell of NAcc is a linear function of the concentration of the sucrose solution the rat consumes [38,39]. Such results suggest that DA release in NAcc mediates sucrose consumption, possibly playing an integral role in the neural basis of reward obtained from sucrose [40].

What is known about DA release in NAcc of the selectively-bred rats used in this study? As summarized above, HYPER, SwHi, and RES rats showed CMS-induced decreases in sucrose consumption and preference for sucrose (vs. water). In our article that reported measurement of monoamine levels and relevant metabolites in different brain regions of our selectively-bred rat lines [26], we found that HYPER (males only

Table 3
Effect of Chronic Mild Stress regimen (CMS) on the different measures assessed — Summary of results for all Rat Lines.

Rat line	Sucrose intake (all days)	Sucrose intake (first days only)	Preference for sucrose (all days)	Preference for sucrose (first days only)	Food intake	Dark phase motor activity
Non-selected (female)	No effect	No effect	No effect	No effect	**Decrease**	No effect
Non-selected (male)	No effect	No effect	No effect	No effect	**Decrease**	Decrease
HYPER (female)	**Decrease***	**Decrease**	**Decrease***	Decrease†	No effect	No effect
HYPER (male)	Decrease*	**Decrease***	Decrease†	**Decrease***	**Decrease**	No effect
SUS	No effect	No effect	No effect	No effect	Decrease	**Decrease**
RES	No effect	Decrease	No effect	**Decrease†**	No effect	No effect
SwHi	**Decrease***	**Decrease***	**Decrease***	**Decrease†**	Increase*	**Decrease***
SwLo	No effect	No effect	No effect	No effect	No effect†	**Decrease†**

"Decrease" or "Increase" or "No effect" within the Table describes how CMS affected rats of the line named in the first column at left with respect to the measure shown at the top of the column. Designation of "Decrease" or "Increase" in boldface indicates that this change was statistically significant, while the designation of "Decrease" or "Increase" in non-boldface indicates that the change approached significance. Next to designations, * indicates a significant difference or † indicates a difference approaching significance when this effect of stress on the rat line is compared with the effect of stress on the Non-selected rats for this measure, which is based on the stress × rat line interaction in the ANOVA comparing the two rat lines on the measure.

analyzed in that study), SwHi, and RES rats showed a significantly reduced ratio of the metabolite HVA to the level of DA in NAcc relative to NS rats and the other selectively-bred lines of rats, thereby indicating that release of DA of NAcc was lower in these three lines than in NS rats and in the other rat lines. Interestingly, it is these three rat lines that show decreases in affinity for sucrose as a consequence of exposure to CMS. Thus, assuming the DA release in NAcc is important for mediating sucrose intake, our data with respect to DA release in NAcc of the various rat lines points to a vulnerability to reduced sucrose uptake/preference of the three lines that in fact showed this effect in response to CMS.

Also with regard to the interplay between DA and sucrose, marked changes in ambulatory activity were often observed during the 3-day periods when animals were able to ingest sucrose, likely produced by stimulation of DA by intake of sucrose. During periods when sucrose was available, dark phase motor activity would sometimes increase, or even "spike" upward markedly, returning to a normal level of activity for that rat line when sucrose was no longer available. Insofar as DA release in forebrain (NAcc and striatum) stimulates motor activity, it appears that sucrose ingestion, by stimulating DA release, also caused increases in ambulatory activity. (Such sucrose-induced increases in ambulatory activity can be discerned in Figs. 7 and 8; this can be discerned by comparing activity during sucrose administration periods to activity of the different lines of animals in periods immediately before and after sucrose administration.) Spiking of activity was most pronounced in female rats and the male SwHi rats. Interestingly, sucrose-induced activity increases, and spiking, were often suppressed by CMS. In non-stressed female NS, both NS and HYPER rats, spiking was evident during the first period of sucrose administration during CMS, and was suppressed by CMS at this time; in the second sucrose administration period, however, stress (CMS) actually accentuated spiking in the NS females (but not in HYPER females). Despite the late effect seen in female NS rats, CMS generally blocked the increases in ambulatory activity otherwise produced by sucrose administration. Not only does CMS usually block sucrose-induced activity increases and "spiking," but it can also be seen that when CMS is removed, activity increases. In particular, during the 3-day periods of sucrose administration, activity of stressed (CMS-treated) rats often increased on the third day of these periods when no stressor was given (note "None" designation for stressor in Figures). In summary, ingestion of the 2% sucrose solution often caused ambulatory activity in the home cage to increase, and even produced marked upward "spiking" of ambulatory activity in female rats and male SwHi rats. The usual effect of CMS was to block increases in home-cage ambulatory activity produced by sucrose ingestion.

5. Conclusion

In conclusion, the present study found that three of the selectively-bred rat lines we tested for their responsiveness to a CMS procedure showed larger decreases in consumption of a palatable sucrose solution and reduced preference for sucrose (i.e., increased tendency to consume water vs. sucrose) than did randomly-bred "normal" Sprague–Dawley rats. The rat lines showing this were HYPER, both females and males, SwHi, and RES. This suggests that certain selectively-bred rat lines examined here are more susceptible than randomly-bred Sprague–Dawley rats to showing a CMS-induced decrease in the principal measure used in CMS studies — sucrose intake and preference for sucrose. Extrapolating to humans, such results can be said to suggest that stress may produce depressive symptoms related to anhedonia more readily in people who have a genetic predisposition to depression than is the case in people who do not have this genetic predisposition.

However, it should be pointed out that a distinct shortcoming of the results reported here relative to the effect that CMS is proposed to have is that CMS-induced decreases in sucrose consumption and decreases in preference for sucrose even in the affected rat lines were small. For example, in no case was there any decrease in preference that approached a definitive loss of preference for sucrose; all rats still vastly preferred the sucrose solution to water even during the CMS procedure. Thus, an effect of the magnitude reported by Strekalova et al. [5] and Pucilowski et al. [6] was not reproduced in this study. Consequently, while success in reducing sucrose consumption and the preference for sucrose by applying CMS to selectively-bred rats was achieved in the study reported here, the effect was never a large one, and preference for sucrose might have been reduced but it was not abolished by the CMS procedure.

Acknowledgments

This work was supported by the Theodore and Vada Stanley Foundation of the National Alliance for the Mentally Ill (NAMI).

References

[1] Katz RJ, Roth KA, Carroll BJ. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neurosci Biobehav Rev 1981;5:247–51.
[2] Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol Biochem Behav 1982;16:965–8.
[3] Willner P, Towell A, Sampson D, Sophokleous S, Muscat R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology 1987;93:358–64.
[4] Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev 1992;16:525–34.
[5] Strekalova T, Spanagel R, Bartsch D, Henn FA, Gass P. Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. Neuropsychopharmacology 2004;29:2007–17.
[6] Pucilowski O, Overstreet DH, Rezvani AH, Janowsky DS. Chronic mild stress-induced anhedonia: greater effect in a genetic rat model of depression. Physiol Behav 1993;54:1215–20.

[7] Valverde O, Smadja C, Roques B, Maldonado R. The attenuation of morphine-conditioned place preference following chronic mild stress is reversed by a CCK_B receptor antagonist. Psychopharmacology 1997;131:79–85.
[8] Nielson C, Arnt J, Sanchez C. Intracranial self-stimulation and sucrose intake differ as hedonic measures following chronic mild stress: interstrain and interindividual differences. Behav Brain Res 2000;107:21–33.
[9] Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 1997;134:319–29.
[10] Brady JP, Thornton DR, deFisher D. Deleterious effects of anxiety elicited by conditioned preaversive stimuli in the rat. Psychosom Med 1962;24:590–5.
[11] Pare WP. The effect of chronic environmental stress on stomach ulceration, adrenal function and consummatory behavior in the rat. J Psychol 1964;57:143–51.
[12] Pare WP. Stress and consummatory behavior in the albino rat. Psychol Rep 1965;16:399–405.
[13] Weiss JM. Effects of coping responses on stress. J Comp Physiol Psychol 1968;65:251–60.
[14] Baker S, Kentner A, Konkle A, Barbagallo L, Bielajew C. Behavioral and physiological effects of chronic mild stress in female rats. Physiol Behav 2006;87:314–22.
[15] Sampson P, Willner P, Muscat R. Reversal of antidepressant action by dopamine antagonists in an animal model of depression. Psychopharmacology 1991;104:491–5.
[16] Duncko R, Kiss A, Skultetyova I, Rusnak M, Jezova D. Corticotropin-releasing hormone mRNA levels in response to chronic mild stress rise in male but not in female rats while tyrosine hydroxylase mRNA levels decrease in both sexes. Psychoneuroendocrinology 2001;26:89.
[17] Forbes NF, Stewart CA, Matthews K, Reid IC. Chronic mild stress and sucrose consumption: validity as a model of depression. Physiol Behav 1996;60:1481–4.
[18] Hatcher J, Bell D, Reed T, Hagan J. Chronic mild stress-induced reductions in saccharin intake depend upon feeding status. J Psychopharmacol 1997;11:331–8.
[19] Konkle A, Baker S, Kentner A, Barbagallo L, Merali Z, Bielajew C. Evaluation of the effects of chronic mild stressors on hedonic and physiological responses: sex and strain compared. Brain Res 2003;992:227–38.
[20] Matthews K, Forbes N, Reid I. Sucrose consumption as an hedonic measure following chronic unpredictable mild stress. Physiol Behav 1994;57:241–8.
[21] Pothion S, Bizot J, Trovero F, Belzung C. Strain differences in sucrose preference and in the consequences of unpredictable chronic mild stress. Behav Brain Res 2004;155:135–46.
[22] Bielajew C, Konkle ATM, Merali Z. The effects of chronic mild stress on male Sprague–Dawley and Long Evans rats. Behav Brain Res 2002;136:583–92.
[23] Griffiths J, Shanks N, Anisman H. Strain-specific alterations in consumption of a palatable diet following repeated stressor exposure. Pharmacol Biochem Behav 1992;42:219–27.
[24] Overstreet DH. Selective breeding for increased cholinergic function: development of a new model of depression. Biol Psychiatry 1986;21:49–58.
[25] Weiss JM, Boss-Williams KA, Moore JP, West CHK. Testing the hypothesis that locus coeruleus hyperactivity produces depression-related changes via galanin. Neuropeptides 2005;39:281–7.
[26] Weiss JM, West CHK, Emery MS, Bonsall RW, Moore JP, Boss-Williams KA. Rats selectively-bred for behavior related to affective disorders: proclivity for intake of alcohol and drugs of abuse, and measures of brain monoamines. Biochem Pharmacol 2008;75:134–59.
[27] Scott PA, Cierpial MA, Kilts CD, Weiss JM. Susceptibility and resistance of rats to stress-induced decreases in swim-test activity: a selective breeding study. Brain Res 1996;725:217–30.
[28] West CHK, Weiss JM. A selective test for antidepressant treatments using rats bred for stress-induced reduction of motor activity in the swim test. Psychopharmacology 2005;182:9–23.
[29] Weiss JM, Cierpial MA, West CHK. Selective breeding of rats for high and low motor activity in a swim test: toward a new animal model of depression. Pharmacol Biochem Behav 1998;61:49–66.
[30] West CHK, Weiss JM. Effects of antidepressant drugs on rats bred for low activity in the swim test. Pharmacol Biochem Behav 1998;61:67–79.
[31] Reid I, Forbes N, Stewart C, Matthews K. Chronic mild stress and depressive disorder: a useful new model? Psychopharmacology 1997;134:365–7.
[32] Hagan JJ, Hatcher JP. Revised CMS model. Psychopharmacology 1997;134:354–6.
[33] Ayensu WK, Pucilowski O, Mason GA, Overstreet DH, Rezvani AH, Janowsky DS. Effects of chronic mild stress on serum complement activity, saccharin preference, and corticosterone levels in flinders lines of rats. Physiol Behav 1995;57:165–9.
[34] Klein D. Differential diagnosis and treatment of the dysphorias, in depression: behavioral, biochemical, clinical and treatment concepts. New York: Spectrum; 1975 .
[35] Papp M. Chronic mild stress. Curr Protoc Pharmacol 1998:5.9.1–8.
[36] Hajnal A, Norgren R. Accumbens dopamine mechanisms in sucrose intake. Brain Res 2001;904:76–81.
[37] Smith G, Smith J. The inhibitory potency of SCH 23390 and raclopride on licking for sucrose increases across brief-access tests. Physiol Behav 2010;101:315–9.
[38] Hajnal A, Smith G, Norgren R. Oral sucrose stimulation increases accumbens dopamine in the rat. Am J Physiol Regul Integr Comp Physiol 2004;286:R31–7.
[39] Liang N, Hajnal A, Norgren R. Sham feeding corn oil increases accumbens dopamine in the rat. Am J Physiol Regul Integr Comp Physiol 2006;291:R1236–9.
[40] Hajnal A, Norgren R. Taste pathways that mediate accumbens dopamine release by sapid sucrose. Physiol Behav 2005;84:363–9.