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

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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.

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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

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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.