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Enhanced corticosterone release after a modified forced swim test in Fawn hooded rats is independent of rearing experience

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Abstract

Recent findings have demonstrated that Fawn hooded (FH/Har) rats exhibit enhanced plasma corticosterone (CORT) responses compared to Wistar rats after exposure to an open field, whereas this effect was not influenced by early social experience. In contrast, it was found that behavior in a modified version of the Porsolt Forced Swim Test (Porsolt FST) was affected by both strain and social experience. An important part of this study included modifications of the Porsolt FST that allowed separation of multiple behavioral endpoints. The present experiment was conducted to determine if FH/Har rats also exhibit enhanced CORT responses after exposure to the modified forced swim test, and whether CORT levels might predict the behavioral response in this context. After the initial exposure in the modified forced swim test FH/Har rats had higher CORT levels than Wistar rats, but this difference was not affected by isolation rearing. However, CORT levels were not correlated with the main behavioral measures assayed in this test. Nonetheless, the data confirm that FH/Har rats have altered HPA axis responses to stressors. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Isolation rearing; Forced swim test; Fawn hooded rats; Stress; Corticosterone; Anxiety

1. Introduction

Recent work has demonstrated differences in anxiety (Hall et al., 1998b, 2000) and HPA axis function (Altemus et al., 1994; Hall et al., 2000) between the Fawn hooded rat (FH/Har) and Wistar rats. Although it appears that both substrains of FH rats, the FH/Har substrain (Hall et al., 1998c) and the FH/Wjd substrain (Rezvhani et al., 1990), have greater consumption of ethanol relative to control strains, the FH/Har rat exhibits greater consumption of low-concentration ethanol while the FH/Wjd rat exhibits increased consumption of 10% ethanol after a period of forced consumption. In addition to these differences, there appear to be quite different behavioral phenotypes in these two substrains (Hall et al., 1998b,c; Overstreet and Rezvani, 1996; Overstreet et al., 1992; Rezvhani et al., 1990). This paper shall refer largely to research in the FH/Har substrain, as it is the subject of the present experiments.

Both FH substrains exhibit a syndrome of effects that may be related to changes in serotonergic function (Aulakh et al., 1994; Overstreet et al., 1992), although the precise relationship of the neurochemical changes in these strains and the behavioral phenotypes associated with FH/Har and FH/Wjd rats has yet to be determined precisely. For instance, it remains to be seen whether increased anxiety in FH/Har rats, as assessed by experimental paradigms such as the elevated plus maze (Hall et al., 1998b) or the open field (Hall et al., 2000), lead to increased HPA axis function (Hall et al., 2000) and self-medication (e.g., increased voluntary ethanol consumption) or whether increased HPA axis reactivity is directly responsible for increased behavioral indices of anxiety. In this case a strong correlation would be expected to exist between CORT and behavioral measures indicative of anxiety or stress.

In what may be a related phenomenon, FH/Har rats exhibit alterations in behavior in a modified version of the Porsolt Forced Swim Test (Hall et al., 1998a). The standard procedure shall be referred to as the Porsolt Forced Swim

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Test (Porsolt FST) and the modified version as the modified Forced Swim Test (modified FST). In the previous study, modifications to the Porsolt FST were made in order to separately determine differences in general activity and escape behavior. This was necessary because of the aforementioned differences in HPA reactivity and anxiety, as well as increased locomotor activity (Fong et al., 1998; Hall et al., 1998b, 2000) in FH/Har, relative to Wistar rats. Ever since the initial conception of the Porsolt FST (Porsolt et al., 1977) general activity level has always been a potential confound for antidepressant effects as exemplified by the effects of locomotor stimulants in the Porsolt FST. This is also a confounding factor if the research goal is to examine different experimental groups that exhibit different levels of locomotor activity as well as potential changes in emotional reactivity (Hall et al., 1998b, 2000). Although this confound has long been recognized, only recently have more extensive behavioral analyses been made in an attempt to separate potential locomotor activity differences from changes in emotional reactivity by modifying the Porsolt FST (Armario et al., 1988; Cervo and Samanin, 1991; Detke et al., 1995; Hall et al., 1998a). In the traditional test (Porsolt et al., 1977) the rats could touch the bottom of the small-diameter cylinder. Recent modifications, which have examined a wider range of behavior, used deeper water (Cervo and Samanin, 1991; Detke et al., 1995; Hall et al., 1998a) and a larger cylinder diameter (Hall et al., 1998a; Nishimura et al., 1988). The greater cylinder diameter made more movement possible, allowing the separation of different forms of active behavior. Thus, in addition to the traditional "immobility" measure, "struggling" behavior was assessed as a putative measure of "despair," and "swimming" behavior was assessed as a putative measure of general activity. Data suggests that a wide range of stimulant drugs selectively increase swimming behavior but not struggling in the modified FST (Hall et al., 1997).

Using this paradigm it was found that FH/Har rats exhibit more active behavior, when compared to Wistar rats, in the modified FST (Hall et al., 1998a). In addition, the nature of this active behavior was dependent on prior rearing experience. Briefly, isolation rearing produces a syndrome of effects that is similar in some respects to the differences observed between FH/Har and Wistar rats (see Robbins et al., 1996; Hall, 1998 for review). In the modified FST FH/Har isolates exhibited increased swimming, while FH/Har socials exhibited increased struggling relative to Wistar controls (Hall et al., 1998a). Moreover, FH/Har rats have an enhanced CORT response to open-field exposure compared to Wistar rats, and this enhancement is greater in FH/Har socials than in FH/Har isolates (Hall et al., 2000). This enhanced HPA axis reactivity might account for increased struggling behavior in FH/Har socials in the forced swim test if this measure is indicative of emotional reactivity.

Thus, the present experiment was conducted with two goals in mind: (1) to determine the generality of enhanced CORT responses in FH/Har rats and how this might interact with isolation rearing; (2) to determine whether CORT responses in the modified FST are related to particular behavioral responses.

2. Method

2.1. Animals

Subjects were FH/Har (National Cancer Institute, NCI, Frederick, MD; $n=9$ isolation-reared, $n=8$ socially reared) and outbred Wistar (Charles River, Frederick, MD; $n=9$ isolation-reared, $n=10$ socially reared) male rats, received on postnatal day 21 and randomly divided into rearing conditions — socially reared versus isolation reared. All subjects were housed in the same room with a 12:12 light:dark cycle and ad-libitum food and water. Socially reared animals were housed two per 45 × 20 × 20 cm cage. Isolation-reared subjects were housed singly in 20 × 20 × 20 cm cages. All subjects could see, hear and smell other rats so that isolation only prevented physical contact. Experimentation began after 12 weeks of these housing conditions. The procedures followed were conducted in accordance with all NIAAA and National Institutes of Health (NIH) ACUC guidelines.

2.2. Procedure

The experiment departed in some respects from the standard Porsolt FST procedure (Porsolt et al., 1977) and from that previously used in our laboratory (Hall et al., 1998a). Unlike the previous report, the rats were only tested once, and then sacrificed. As in the previous report, the rats were placed in a cylindrical tank (Nalgene; diameter 50 cm), filled to a depth of 40 cm with 25°C water. The rats remained in the water for 15 min, at which time the rats were towel dried and removed to another room for immediate decapitation and collection of trunk blood. These trials were videotaped for later analysis.

All rats were sacrificed by decapitation between 1000 and 1400 h. Trunk blood was collected in 3-ml tubes containing EDTA (Becton Dickinson, Franklin Lakes, NJ) and stored on ice. The tubes were centrifuged at 3000 rpm for 15 min and aliquots of plasma were frozen at -70°C for subsequent analysis of CORT levels using a radioimmunoassay kit (ICN Biomedicals, Costa Mesa, CA). One week prior to the FST the rats were removed from the home cage, placed in a restraining device and blood collected for determination of baseline CORT levels. The tip of the tail was removed with a sterile razor blade and blood (200 μl) was collected using Microvette capillary collection vials (Sarstedt, Germany) containing EDTA. These samples were analyzed for CORT as previously described. The entire collection procedure lasted less than 30 s.

The videotaped test sessions were scored by two observers who were blind to the rearing conditions (but not strain since there is an obvious coat color difference). Each observer independently assessed the duration of immobility, swimming, and struggling using a behavioral scoring program (TIMER) developed at the NIH. The scores reported are the average of the two observers' scores. Immobility was defined as being stationary with only enough motion of the tail or forepaws to keep the head above water. Usually the forepaws remained at the side of the animals. Swimming was defined as active use of the forepaws with forward movement, in the center or along the sides of the cylinder, which did not involve lifting the paws above the surface of the water. Struggling was defined as active pawing of the sides of the cylinder, lifting the paws above the surface of the water. The frequency of diving and headshakes, both unnecessary to define, were also scored. Diving was uncommon, so the duration was not scored separately from the duration of swimming. In a previous study (Hall et al., 1998a) it was thought that these groups might differ on these latter behavioral measures as well, although they were not recorded.

2.3. Data analysis

The behavioral data were analyzed by ANOVA with the between-subjects factors of Rearing (isolation-reared vs. socially reared), and Strain (Wistar vs. FH/Har). The corticosterone (CORT) data were analyzed by ANOVA with between-subjects factors of Rearing and Strain, and the within-subjects factor of Stimulation (basal vs. stimulated CORT levels).

Additionally, individual correlations between baseline and stimulated CORT values and the behavioral variables were determined using all data points independent of group. Significant correlations were then assessed separately for each group defined by a significant variable identified in the ANOVA.

3. Results

3.1. Behavior

FH/Har rats had a significantly shorter duration of immobility than Wistar rats, Strain: $F(1,32)=5.6$, $P<.05$; Fig. 1A. This decrease in immobility was accompanied by increases in swimming duration in FH/Har rats relative to Wistar rats, Strain: $F(1,32)=4.9$, $P<.01$; Fig. 1B. Rearing condition was without effect on either immobility, Rearing: $F(1,32)=1.6$, ns, or swimming, Rearing: $F(1,32)=0.02$, ns. Struggling duration was unaffected by either Strain, $F(1,32)=0.8$, ns; Fig. 1C, or Rearing, $F(1,32)=0.3$, ns. A portion of the increase in swimming in FH/Har rats may have been due to increased diving. The frequency of diving was elevated in FH/Har rats relative to Wistar rats, Strain: $F(1,32)=5.0$, $P<.05$; Fig. 1D. Again, Rearing, $F(1,32)=0.1$, ns was without effect on this measure. Headshakes were elevated in FH/Har rats relative to Wistar rats, Strain: $F(1,32)=22.5$, $P<.01$; Fig. 1D, and in isolation-reared rats relative to socially reared rats, Rearing: $F(1,32)=4.2$, $P<.05$.

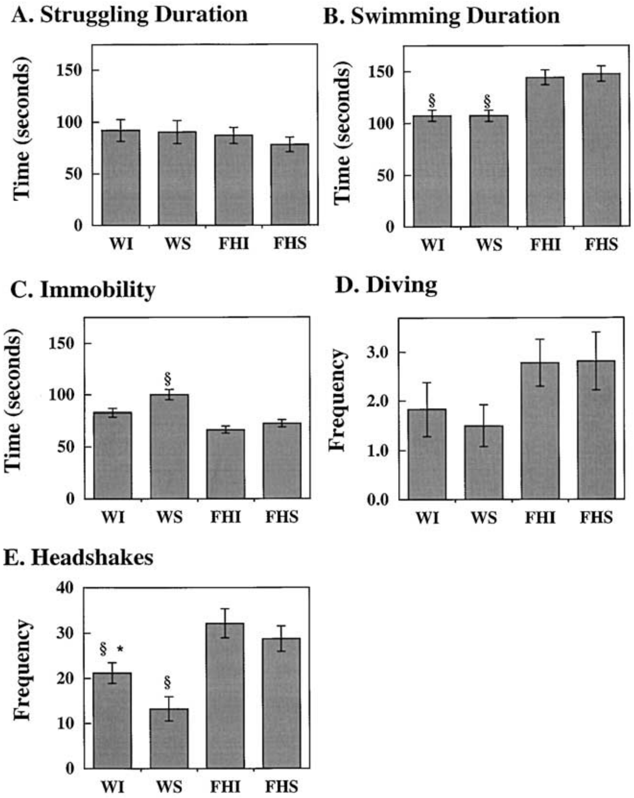

Fig. 1. Duration of behavior in seconds from the modified FST, (A) immobility, (B) swimming, and (C) struggling, and the frequency of (D) diving, and (E) headshakes, for Fawn hooded socials (FHS), Fawn hooded isolates (FHI) and Wistar isolates (WI) and Wistar socials (WS). Data are expressed as mean ± standard error of the mean. (*) Significant post hoc difference between rearing groups by *t* test ($P<.05$; FHI vs. FHS, or WI vs. WS). (§) Significant post hoc difference by *t* test ($P<.05$) between strains (FHI vs. WI, or FHS vs. WS).

3.2. Plasma corticosterone

Baseline levels of CORT were not affected by either Strain or Rearing (Fig. 2). The tail sampling procedure used in this experiment was not particularly stressful, at least at the point when the sample was taken, producing values of baseline CORT in the range of 10 to 25 ng/ml. The forced swim produced substantial and significant increases in CORT levels, Stimulation: $F(1,32)=433.0$, $P<.001$. FH/Har rats had higher levels of CORT than Wistar rats after the forced swim. This resulted in a significant overall effect of Strain, $F(1,32)=10.0$, $P<.01$, and a significant interaction between Strain and Stimulation in the ANOVA, $F(1,32)=6.5$, $P<.05$.

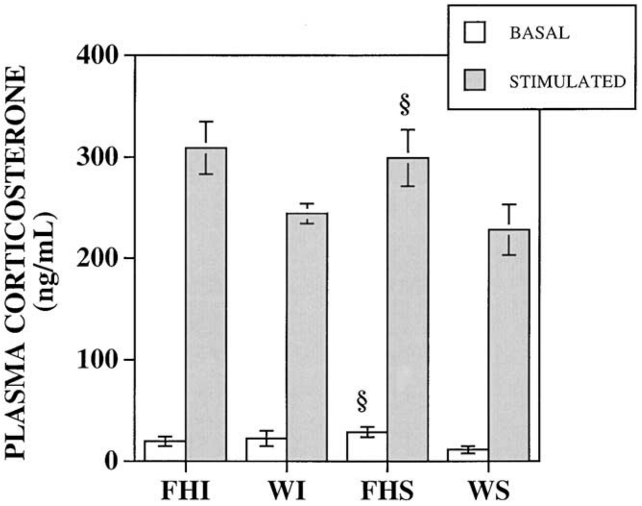

Fig. 2. Baseline (BAS) and stimulated (STIM) CORT levels in Fawn hooded isolate (FHI), Fawn hooded social (FHS), Wistar isolate (WI), and Wistar social (WS) rats. The data are expressed as mean ± S.E.M. All differences between baseline and stimulated conditions significant by post hoc *t* test ($P<.05$). (*) Significant post hoc difference by *t* test ($P<.05$) between rearing groups. (§) Significant post hoc difference by *t* test ($P<.05$) between strains.

3.3. Relationship of plasma corticosterone to behavior in the forced swim test

Baseline CORT levels were not correlated with any behavioral measures. Stimulated CORT levels were not correlated to most behavioral variables. Indeed, contrary to the hypothesis, struggling duration was not correlated with stimulated CORT levels ($r=-.11$, ns), nor was immobility ($r=-.06$, ns). The only behavioral measure that was significantly correlated with stimulated CORT levels was diving frequency ($r=.44$, $P<.01$). Since diving frequency was significantly affected by Strain, separate correlations were determined for FH and Wistar rats, independent of rearing. There was a significant correlation between stimulated CORT levels and diving for FH rats ($r=.55$, $P<.03$) but not Wistar rats ($r=.12$, ns).

4. Discussion

As in a previous study (Hall et al., 1998a), substantially less immobility was observed in FH/Har rats in the modified FST compared to Wistar rats, and no differences in immobility were attributable to isolation rearing. This is consistent with findings in FH/Har rats (Hall et al., 1998a; Lahmame et al., 1996), but different from FH/Wjd rats (Overstreet et al., 1992). This latter study used a modified FST method that was similar to the procedure used here, analyzing only the first forced swim, usually a preexposure in the more standard Porsolt FST. Thus, the different effects on immobility in the FH substrains are not the result of analyzing the first FST rather than the second FST. However, it must be noted that the amount of immobility observed in this report, approximately 60 to 100 s, was less than that observed in our previous report (Hall et al., 1998a), approximately 100 to 150 s. Thus, the rats in the present study, analyzing the first swim, were more active, which was reflected largely by increased swimming. In our previous study (Hall et al., 1998a) the duration of swimming was in the range of 40 to 60 s while in the present report in was in the range of 100 to 150 s. A direct comparison will be necessary to confirm whether these differences are the result of analyzing the first rather than the second FST.

The two substrains of FH rats (FH/Har from the NCI; FH/Wjd from the University of North Carolina, Chapel Hill) appear to have different, though perhaps related, behavioral syndromes. However, direct comparisons between FH rats from both colonies have been lacking and are necessary before any strong conclusions may be drawn about substrain differences. There do appear to be differences in both alcohol consumption and anxiety between these substrains (Overstreet and Rezvani, 1996), but this study did not compare the FH substrains to any other standard strains so it was not possible to tell which strain was altered relative to the usual controls, and both strains appear to be different on some measures relative to these control strains (usually outbred Wistar or Sprague-Dawley rats).

With regard to FH/Har rats, contrary to a previous report (Hall et al., 1998a), although active behavior was increased in FH/Har rats in the present study, no differences were observed between isolation-reared and socially reared FH/Har rats in the type of active behavior (swimming vs. struggling) that was increased. FH/Har rats, independent of rearing condition, exhibited more swimming behavior than Wistar rats. This difference might be the result of the aforementioned methodological considerations (analyzing the first vs. second swim). It is possible that rearing effects may only be observed in the second swim, after more habituation or learning has occurred, that is, after an expectation of being removed from the apparatus has been formed.

During that previous study (Hall et al., 1998a) casual (unreported) observations of diving and head-shaking behavior were noted that appeared to be more frequent in some groups than in others. These differences were confirmed in the present study, although the meaning of these behavioral measures is uncertain. Diving is a rare behavioral occurrence in the FST. However, substantial diving, to the point where the rats must be removed for their safety, is observed after administration of MK801 (Hall et al., 1997). The enhanced headshakes observed in the FST may be the result of increased 5-HT$_{2A}$ receptors in FH/Har, relative to Wistar rats, and in isolation-reared rats relative to socials. Increased 5-HT$_2$ receptor binding has been observed in FH/Har rats (Hulihan-Giblin et al., 1992), and increased frequency of "wet dog" shakes induced by quipazine in FH/Wjd rats (Gudelsky et al., 1985). 5-HT$_{2A}$ receptor stimulation is associated with headshakes (Peroutka et al., 1981), and repeated treatment with CORT enhances headshakes induced by 5-HT$_{2A}$ receptor agonists (Berendsen et al., 1996). Thus, increased head shakes in FH/Har rats is consistent with the enhanced activity of the HPA axis in these rats observed previously (Hall et al., 2000), and in the present study. It is not surprising that there was no relationship between acute CORT responses and headshakes as the putative change in 5-HT$_{2A}$ receptors would be the result of long-term effects of enhanced CORT responsiveness. Similarly, the early rearing experience of isolates, resulting in repeated elevations of CORT, enhances 5-HT$_2$ responsivity, although not "wet dog" shakes (Wright et al., 1991).

Generally speaking isolation rearing has not been found to permanently alter HPA axis reactivity, as do other types of social deprivation (see Hall, 1998 for review). Thus, this experiment is consistent with the isolation-rearing literature. However, a caveat is that one study found that isolation rearing does not alter maximal CORT release but instead alters recovery to basal values, producing prolonged CORT elevations after a stressful experience (Plaut and Grota, 1971). Such an alteration in feedback inhibition would be missed in the present study (and much of the isolation-rearing literature that has examined short endpoints). Differences in feedback inhibition might influence latter behavior (e.g., in the usual paradigm, the second swim). So, although behavioral differences resulting from isolation rearing observed a first forced swim are not associated with changes in CORT function, it is possible that changes in behavior in a subsequent forced swim might be influenced by prolonged elevations of CORT levels. A different experimental design would be necessary to examine this hypothesis.

Contrary to the initial hypothesis, neither struggling behavior nor immobility were correlated with stimulated CORT levels. This would seem to indicate that the behavioral mechanisms mediating escape behavior, or behavioral "despair," are distinct from those that mediate CORT responses. However, the conclusion is weakened by the failure to observe group differences in struggling behavior. It remains possible that under other circumstances (e.g., the second swim) there may be a relationship between CORT and behavior in the modified FST. That is, perhaps initial CORT levels, or the levels after the experience as CORT is returning to baseline, influence learned behavioral responses and are correlated. In any case, in the present circumstance, diving behavior was correlated with stimulated CORT levels. The meaning of this correlation is unknown, but may indicate a relationship between CORT release and glutamate function. Modulators of glutamate function such as the glycine antagonist HA-966 decrease behavioral responses to stress (Goldstein et al., 1994), and CORT potentiates glutamate release (Stein-Behrens et al., 1992, 1994). Though highly speculative, this may indicate that there is decreased glutamate response to CORT in FH/Har rats relative to the control strain.

The main finding of this study is that FH/Har rats have greater CORT responses in the modified FST, just as they have greater CORT responses in the open field (Hall et al., 2000), but isolation-reared rats do not. It has previously been reported that there are no baseline differences in CORT (Altemus et al., 1994; Hall et al., 2000). In the one study that reported elevated "baseline" CORT (Aulakh et al., 1988), the "baseline" condition involved saline injection and placement in a novel box, so really reflects enhanced stimulated CORT consistent with the present study and our previous observations (Hall et al., 2000). One other study has examined stimulated CORT using a tail cut procedure (Lahmame et al., 1996), and found a trend toward greater CORT reactivity in FH/Har rats. Hyperresponsiveness of CORT to stressful stimuli is consistent with enhanced anxiety (Hall et al., 1998b, 2000) and the suggestion that FH/Har rats may constitute an animal model of anxiety (Altemus et al., 1994).

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