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Responses to Novelty Stress in Female F344 Rats: Effects of Age and *d*-Fenfluramine Treatment

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HANDA, R. J., M. GEORGE, B. H. GORDON, D. B. CAMPBELL AND S. A. LORENS. *Responses to novelty stress in female F344 rats: Effects of age and* d-*fenfluramine treatment.* PHARMACOL BIOCHEM BEHAV **53**(3) 641–647, 1996.—To elucidate some of the mechanisms underlying the neuroendocrine and neurochemical changes associated with age in female rats, we administered the serotonin (5-HT) releaser and reuptake inhibitor, *d*-fenfluramine (*d*-FEN; 0.0 or 0.6 mg/kg/day, PO) for 30–38 days to young (4 month) and old (21 month) F-344 female rats. Animals were placed into a novel open field (OF) for 20 min before sacrifice. Control animals were sacrificed immediately upon removal from their home cage (HC). Old rats exhibited significantly ($p < 0.05$) less exploratory behavior and a smaller CORT response to OF than young animals. *d*-FEN treatment had no effect on plasma ACTH and CORT levels or exploratory behavior. The old HC rats had significantly ($p < 0.05$) higher plasma levels of prolactin (PRL) than the young HC rats. A stress induced increase in PRL secretion was observed in the old rats only, which was attenuated by *d*-FEN treatment. In the OF groups, both the young and old rats showed elevated medial frontal cortex (MFC) dopamine turnover (DOPAC/DA ratio), but only the young rats exhibited an elevation in norepinephrine (NE) turnover (MHPG/NE ratio). *d*-FEN treatment blocked the stress-induced increase in NE turnover in the young rats and the increase in DA turnover in the old rats. These data suggest that 5-HT activity could be involved in the age-related changes in the MFC catecholamine and PRL responses to stress in female rats.

Aging ACTH Corticosterone Dopamine Female F-344 rat *d*-Fenfluramine Medial frontal cortex Norepinephrine Prolactin Serotonin Stress

SEX differences in the hormonal response to stress are well documented (2,3,21). Previous studies have demonstrated that female rats release greater amounts of ACTH and corticosterone (CORT) following a stressor than do males. The sex differences in the hormonal responses to stress are likely a result of differing gonadal steroid hormone levels because the response of female rats to immobilization stress varies across the estrous cycle (30). Furthermore, estrogen treatment augments (5,20,30) and androgen treatment inhibits (7,16) ACTH and CORT responses.

In males, old rats show a) reduced exploratory behavior (2,3,15); b) elevations in basal plasma prolactin (PRL) and ACTH levels (9,15); c) an exaggerated ACTH and CORT response to stress (15,22,27); d) an absence of a PRL response to stress (15); and e) a greater stress-induced increase in medial frontal cortex (MFC) norepinephrine (NE) turnover (15,22). We have found, moreover, that subchronic treatment with the serotonin (5-HT) releaser and reuptake inhibitor, *d*-fenfluramine (*d*-FEN), normalized the ACTH and CORT responses to stress in the old male rats without affecting basal levels in either age group or the young male's response to stress (15). *d*-FEN also blocked the stress-induced increase in MFC NE turnover in both young and old rats, but did not affect MFC dopamine (DA) or 5-HT metabolism. These data suggest that

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increased 5-HT neurotransmission in old male rats prevents the hyperactivation of the hypothalamo-pituitary-adrenal (HPA) axis and the noradrenergic response to stress.

In the present study we compared the neuroendocrine and neurochemical responses to novelty stress of young (5 month) and old (22 month) F344 female rats, and also examined the effects of subchronic *d*-FEN treatment. The F344 rat was used in these studies to allow comparison with our previously published data on the responses of old male F344 rats to stress and *d*-FEN treatment (15). Furthermore, the F344 strain is commonly used in aging studies and is easily obtainable from NIH colonies. Our data demonstrate that the aging female F344 rat shows a unique endocrine and neurochemical response to novelty stress and that these responses are not altered by *d*-FEN in the same fashion as the male.

METHOD

Animals

Female Fischer 344 (F344) rats were obtained from the NIA colony at Harlan Sprague-Dawley Inc. (Indianapolis, IN). On arrival the animals were 3.5 (n = 76) or 20.5 (n = 44) months of age. The animals were housed individually in an illumination (12 L : 12 D cycle; lights on at 0700 h), temperature- (20–22°C) and humidity (50–55%)-controlled American Association for the Accreditation of Laboratory Animal Care (AAALAC) approved environment. All protocols were approved by the IACUC at Loyola University, Chicago.

Procedure

Beginning 2 weeks after their arrival, the animals received *d*-FEN hydrochloride (0.6 mg/kg b.wt./day, PO; Servier, France) in their drinking water for 30–38 days prior to sacrifice. Control animals had ad lib access to unadulterated deionized water. All rats had ad lib access to Purina rat chow. Body weights were recorded every 3 days and 24 h fluid intake was determined daily. The concentration of *d*-FEN in the drinking water was adjusted accordingly.

Beginning 10 days before sacrifice, vaginal smears were performed daily to ensure that the young female rats would be sacrificed either during diestrus or estrus. The old rats were anestrus. On the day of sacrifice, the animals were rapidly decapitated between 0900 and 1200 h either immediately upon removal from their home cage (HC) or 20 min after being placed in a novel environment (open field; novelty stress). Trunk blood was collected into polypropylene tubes containing 0.3 ml of 3 M EDTA and 1000 KIU trasylol (Sigma Chemical Co., St. Louis, MO). Whole blood was centrifuged at 1500 × *g* for 15 min and plasma was removed and frozen at −70°C until assayed for ACTH, CORT, and PRL levels by radioimmunoassay (RIA) as previously described (22). Brains were removed from the skull and dissected over ice. The medial frontal cortex (MFC) and rostral 4.0 mm of the suprarhinal dorsolateral frontal cortex (DLFC) were obtained, frozen on dry ice, and stored at −70°C until assayed, respectively, for monoamines and their metabolites (22) and *d*-FEN and *d*-norfenfluramine (*d*-norFEN) levels (26). Carcasses were examined for any gross pathologic changes.

Behavioral Analysis

Prior to sacrifice, some animals were placed in the open field (OF) and their behavior quantitated for 20 min. The OF measured 100 × 100 × 40 cm high. The floor was painted flat white and divided into nine squares (20 cm sq) by thin black lines. Four equidistantly spaced holes (3.5 cm diameter) were located in the four corner squares of the central nine squares. The OF was located in a sound-attenuated darkened room and illuminated by a 40 W bulb positioned 100 cm over the center of the chamber as well as a 20 W fluorescent bulb located under the elevated floor of the chamber. The animals were placed in the middle of the chamber and allowed to roam free for 20 min prior to sacrifice. Behavior in the open field was videotaped for later analysis. The following parameters were analyzed: a) the number of wall and center squares entered, b) the number of nose pokes (rat inserts its snout into one of the holes), c) the number of rears (rat stands on hind legs and sniffs), and d) the number of fecal boli excreted.

Data Analysis

Data reduction and statistical analysis was performed using the PC ANOVA statistical package (version 1.0; Human Systems Dynamics, Northridge, CA). Initially we only compared the young estrus and diestrus groups using a three-way analysis of variance (ANOVA; cycle stage × stress × drug). Because no effects of estrus cycle stage were obtained on any of the measures, the appropriate diestrus and estrus groups were combined. The hormonal and neurochemical data were analyzed by a three-way ANOVA (age × drug × stress) followed when appropriate by a Newman-Keuls' multiple range test for post hoc comparisons (31). The drug concentrations and open field behavioral data were analyzed by a two-way ANOVA (age × drug) and the body weight and fluid intake measures were analyzed by three-way ANOVA (age × drug × time) with repeated measures across time.

RESULTS

Animals

At the time of sacrifice all of the rats appeared healthy, with the exception of five old rats who had large pituitary tumors (at least 3.0 mm in diameter). These five animals were eliminated from the study. As shown in Table 1, the young rats weighed less than the old rats but drank the same amount of fluid. The *d*-FEN treatment did not affect body weight or fluid intake.

Brain Drug and Metabolite Levels

Old rats had higher DLFC concentrations (Fig. 1) of *d*-FEN (44%) and *d*-norFEN (31%). The ANOVA, however,

TABLE 1

EFFECTS OF SUBCHRONIC *d*-FENFLURAMINE (*d*-FEN) ON MEAN (±SEM) BODY WEIGHTS AND FLUID INTAKES OF YOUNG (5 MONTHS) AND (22 MONTHS) OLD FEMALE F344 RATS

Group	n	Body Weight (g)		Water Intake (ml/24 h)	
		Day 1	Day 30	Day 1	Day 30
Young					
Vehicle	39	198 ± 2	206 ± 2	18 ± 1	22 ± 1
d-FEN	37	194 ± 1	201 ± 2	18 ± 1	22 ± 1
Old					
Vehicle	20	286 ± 4	283 ± 5	21 ± 1	23 ± 1
d-FEN	19	281 ± 4	269 ± 4	18 ± 1	21 ± 1

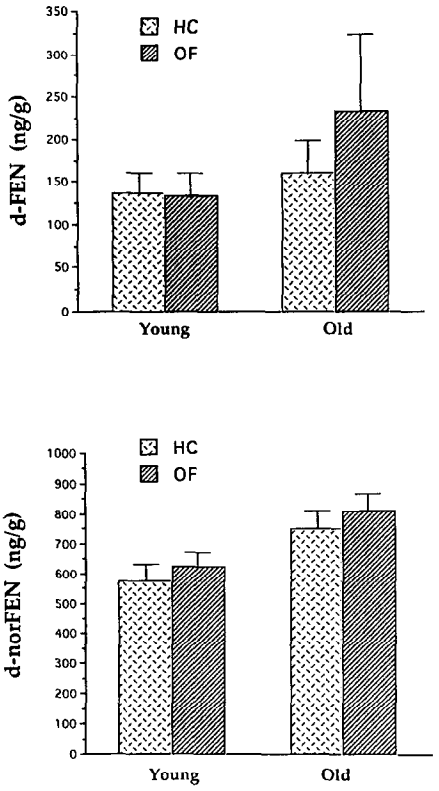

FIG. 1. Dorso-lateral frontal cortex *d*-fenfluramine (upper panel) and *d*-norfenfluramine (lower panel) in young and old female F344 rats following exposure to novelty (open field; OF) for 20 min. Control rats were sacrificed directly out of their home cage (HC). Each bar represents the mean ± SEM of data from 8-19 animals per group.

did not reveal any significant group differences in DLFC *d*-FEN levels. Although a significant, $F(1, 53) = 8.0$, $p < 0.007$, age effect on DLFC *d*-norFEN levels was seen, the post hoc analysis failed to discern any individual group differences. Overall, these data suggest that old female F344 rats clear *d*-norFEN more slowly than young female rats.

Open Field Behavior

Old rats exhibited less exploratory behavior and greater defecation in the OF than the young rats (Fig. 2). *D*-Fen treatment did not affect the OF behavior of either the young or the old rats. Significant age effects were found on the number of a) wall, center, and total squares entered, $Fs(1, 53) = 6.5$-14.1, $p < 0.01$, b) rears, $F(1, 53) = 4.6$, $p < 0.03$, c) nose pokes, $F(1, 53) = 12.0$, $p < 0.001$, and d) fecal boli, $F(1, 53) = 33.2$, $p < 0.00001$. These observations suggest that the novel environment produced a greater fear response in the old rats than in the young animals.

Hormonal Analyses

ACTH. Only the stress effect on plasma ACTH levels was significant, $F(1, 94) = 102.6$, $p < 0.00001$. No effects of *d*-FEN were observed. Although the baseline (HC) ACTH concentrations in the old rats was greater than in the young female rats (Fig. 3), this difference did not reach statistical significance.

CORT. Significant age, $F(1, 99) = 5.9$, $p < 0.02$, stress, $F(1, 99) = 130.0$, $p < 0.00001$, and age × stress, $F(1, 99) = 20.9$, $p < 0.0001$, effects on plasma CORT levels were demonstrated. Post hoc analysis showed that the stress induced increase in CORT in old rats was 20% less than that of young rats (Fig. 4). No effects of *d*-FEN were found.

PRL. Significant age, $F(1, 91) = 96.4$, $p < 0.00001$, stress, $F(1, 91) = 20.3$, $p < 0.0001$, age × stress, $F(1, 91) = 19.9$, $p < 0.0001$, drug × stress, $F(1, 91) = 3.7$, $p < 0.05$, and age × drug × stress, $F(1, 91) = 3.8$, $p < 0.05$, effects on plasma PRL levels were observed. As seen in Fig. 5, the basal levels of PRL were higher in the young than in the old rats. In contrast to the young rats, the old rats showed a significant stress induced increase in PRL secretion, which was attenuated by *d*-FEN treatment (Fig. 5).

MFC Monoamines and Metabolites

DA and metabolites (Table 2). No significant effects were found on MFC DA concentrations. ANOVAs did not reveal any significant drug effects on any of the measures. Significant age, $Fs(1, 106) = 19.5$-20.6, $p < 0.0001$, and stress, $Fs(1, 106) = 33.7$-44.1, $p < 0.00001$, effects were observed

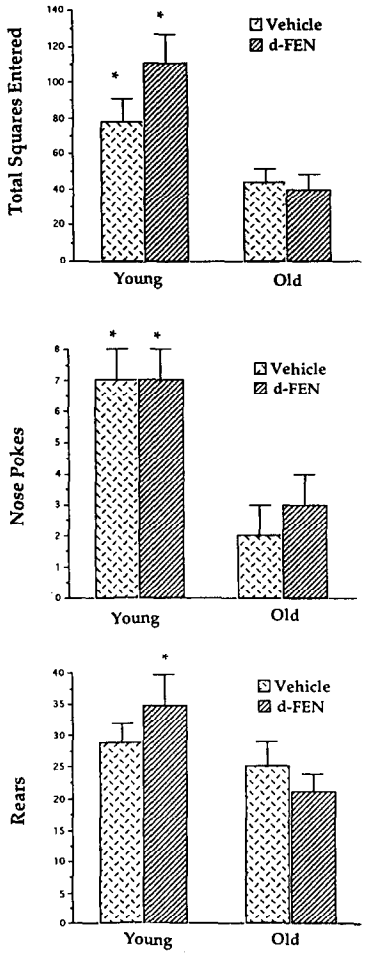

FIG. 2. Behavior in the open field of young and old F344 female rats following vehicle or *d*-fenfluramine (*d*-fen) treatment. Each bar represents the mean ± SEM of 8-20 individuals per group. *Designates those groups that were significantly different from old animals of the same treatment group.

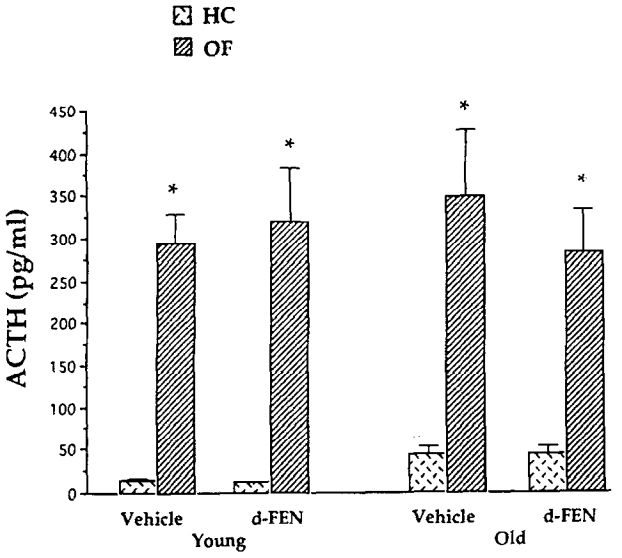

FIG. 3. Plasma ACTH levels in young and old F344 female rats following exposure to novelty (open field, OF). Control rats were sacrificed directly out of the home cage (HC). Animals were treated with *d*-fenfluramine or vehicle for 30–38 days in their drinking water. *Designates those groups with significantly ($p < 0.01$) elevated levels of ACTH vs. home cage controls. Each bar represents the mean ± SEM of 8–20 animals.

on MFC DOPAC and HVA levels, as well as HVA/DA ratios. In addition, a significant, $F(1, 106) = 4.0$, $p < 0.05$, stress × drug interaction was obtained on MFC DOPAC concentrations. Only the stress effect on DOPAC/DA ratios reached significance, $F(1, 106) = 6.5$, $p < 0.01$. Although the old rats exhibited significantly less MFC DOPAC (15%) and HVA (29%), the Newman-Keuls analyses did not reveal any individual group differences between the nonstressed (HC) groups. On the other hand, the post hoc analyses showed that the 20-min exposure to the OF resulted in significant ($p < 0.05$) increases in the MFC DOPAC and HVA levels and DOPAC/DA and HVA/DA ratios in all of the stressed groups, except for the DOPAC concentrations and DOPAC/DA ratios in the old *d*-FEN-treated animals (Table 2).

NE and MHPG (Table 3). No significant effects on MFC NE levels were observed. On the other hand, significant age, $Fs(1, 107) = 12.0$–17.3, $p < 0.001$, and age × drug, $Fs(1, 107) = 4.0$–4.1, $p < 0.05$, effects were obtained on MFC MHPG concentrations and MHPG/NE ratios. An age × stress effect, $F(1, 107) = 6.1$, $p < 0.01$, on MHPG/NE ratios was also observed. The post hoc analyses showed that the MFC MHPG levels and MHPG/NE ratios were higher ($p < 0.05$) in the young vehicle group than in all the other groups. These data suggest that there is an age-related decrease in MFC NE turnover, and that *d*-FEN treatment blocks the stress induced increase in MFC NE turnover.

5-HT and 5-HIAA (Table 3). No significant effects on MFC 5-HT concentrations or 5-HIAA/5-HT ratios were found. Significant age, $F(1, 108) = 4.3$, $p < 0.04$, stress × drug, $F(1, 107) = 7.3$, $p < 0.008$, and age × stress × drug, $F(1, 107) = 4.1$, $p < 0.04$, effects, however, were observed on MFC 5-HIAA content. The post hoc analysis showed that these effects were due to the higher 5-HIAA concentrations in the old vehicle rats exposed to the OF than in the young HC and old OF groups.

DISCUSSION

With these studies we have demonstrated unique age-related changes in the endocrine and neurochemical responses to novelty in the female rat. In comparison to previous studies showing a hyperactivation of the HPA response in aging male rats (15,22,27), our data demonstrate that old F344 female rats show a reduced CORT release in response to novelty stress. Interestingly, young female rats did not respond to novelty with an increase in prolactin secretion. Females also showed an age-related increase in basal prolactin levels and these old females further increased prolactin in response to novelty stress. We have previously reported that subchronic *d*-FEN treatment normalizes the HPA response but not the PRL response of the old males (15). In contrast, *d*-FEN treatment of aging female rats does not alter the CORT response but does attenuate the PRL response to novelty. Neurochemically, old male rats exhibit a greater increase in MFC NE metabolism in response to stress than young animals. In contrast, only young female rats show a stress-induced increase in MFC NE turnover that can be blocked by *d*-FEN treatment.

Previous studies have demonstrated sex differences in the ACTH and CORT response to stressors (2,3,8,21). These studies have shown that, in comparison to males, female rats release greater amounts of ACTH and CORT following a variety of stressors. Furthermore, recent evidence suggests that the higher ACTH and CORT response to stress in females is a result of circulating estrogen titers (5,20,21,30). In con-

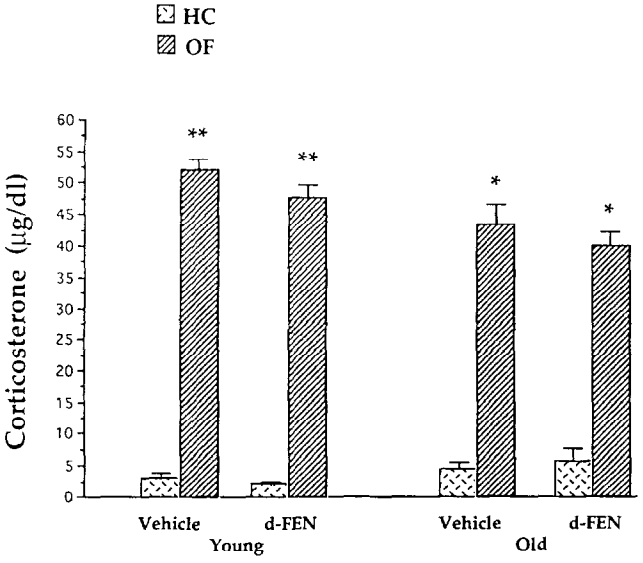

FIG. 4. Plasma corticosterone levels in young and old F344 female rats following exposure to novelty (open field, OF). Control rats were sacrificed directly out of the home cage (HC). Animals were treated with *d*-fenfluramine or vehicle for 30–38 days in their drinking water. * And ** designates those groups with significantly ($p < 0.01$) elevated levels of corticosterone vs. home cage controls. Corticosterone increases in old animals (*) were significantly ($p < 0.02$) less than those of young animals (**). Each bar represents the mean ± SEM of 8–20 animals.

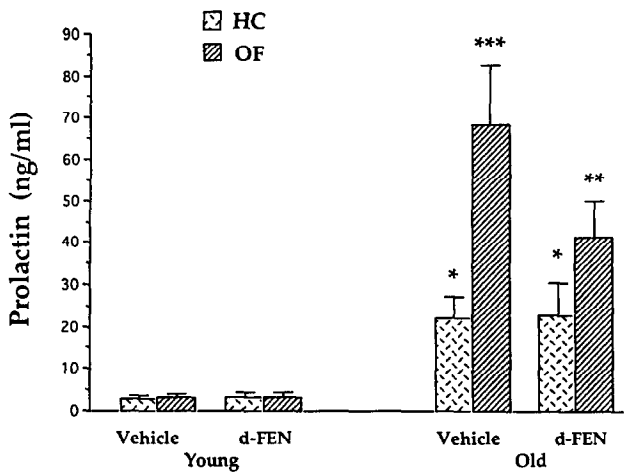

FIG. 5. Plasma prolactin levels in young and old F344 female rats following exposure to novelty (open field, OF). Control rats were sacrificed directly out of the home cage (HC). Animals were treated with *d*-fenfluramine or vehicle for 30–38 days in their drinking water. *** and ** Designates those groups with significantly ($p < 0.01$) elevated levels of prolactin vs. appropriate home cage controls. *** and ** are significantly ($p < 0.05$) different from each other. *Designates those HC groups with significant ($p < 0.01$) increases in prolactin vs. young HC animals. Each bar represents the mean ± SEM of 8–20 animals.

trast, the lower ACTH and CORT response to stress of male rats is in part due to the presence of circulating androgen (7,16).

In these studies, we used the introduction to a novel open field as the stressor/stimulus to examine neuroendocrine and neurochemical end points. This type of psychological stressor has previously been shown to activate hormone secretory systems and induce neurotransmitter turnover in male rats (2,15,22). In addition, this type of stressor allowed us to monitor behavioral end points of the stressor such as activity and exploration, both of which have been suggested as good indices of fear and emotionality (12).

Sex differences in open field behaviors have also been previously reported (1). In all cases, females show greater activity in the open field than males (1). Data from the present study, when compared to that from our previous study using male rats, further supports this sex difference. In contrast to hormone secretory patterns, activity patterns in the open field do not appear to be influenced by gonadal steroid hormone levels in adulthood. Consequently, our observation of decreases in activity in aging female rats cannot be explained by changes in gonadal steroid hormone levels. Decreases in open field activity of old female rats are consistent with increased fear responses (12). However, there was no corresponding increase in the hormonal stress response. Whether age-related increases in stress responsiveness are system, and/or sex specific remains to be determined.

Age-related decreases in CORT secretion in female rats have previously been demonstrated (2,3). These changes are opposite the age-related increases in CORT secretion of male rats following novelty and other stressors, which have been reported by us (15,22) and others (2,3,27). Furthermore, the present study has confirmed and extended the observations of Brett et al. (2,3) by showing that age-related changes in CORT secretion are not accompanied by concomitant changes in ACTH. This suggests that either changes in ACTH responsible for the decreased CORT response in aged females occurs at a time point earlier than the 20 min point that we sampled in these studies, or that the decreases in the CORT response to novelty are a consequence of age-related changes in adrenal sensitivity to ACTH. Changes in adrenal sensitivity to

TABLE 2

CONCENTRATIONS (MEAN ± SEM ng/g OF DOPAMINE AND ITS METABOLITES IN THE MEDIAL FRONTAL CORTEX OF YOUNG (5 MONTH) AND (22 MONTH) OLD FEMALE F344 RATS

Group	*n*	DA	DOPAC	DOPAC/DA	HVA	HVA/DA
Young vehicle						
HC	19	160 ± 3	75 ± 3	0.47 ± 0.03	43 ± 4	0.27 ± 0.02
OF	20	151 ± 9	98 ± 4*	0.73 ± 0.19*	69 ± 5*	0.49 ± 0.06*
Young *d*-FEN						
HC	19	153 ± 5	74 ± 3	0.50 ± 0.04	42 ± 3	0.28 ± 0.02
OF	18	155 ± 6	93 ± 4*	0.63 ± 0.05	70 ± 5*	0.46 ± 0.04*
Old vehicle						
HC	9	147 ± 10	62 ± 5	0.45 ± 0.06	29 ± 5	0.21 ± 0.04
OF	11	153 ± 10	86 ± 5*	0.59 ± 0.06	49 ± 7*	0.36 ± 0.08*
Old *d*-FEN						
HC	11	132 ± 8	68 ± 3	0.55 ± 0.06	28 ± 3	0.23 ± 0.03
OF	8	154 ± 10	71 ± 4	0.49 ± 0.06	54 ± 4*	0.36 ± 0.03*

Rats were treated with vehicle or *d*-fenfluramine (*d*-FEN) for 30–38 days, then sacrificed immediately after removal from their home cage (HC) or 20 min after being placed in a novel open field (OF). Abbreviations: *n* = number of rats/group; DA = dopamine; DOPAC = 3,4-dihydroxyphenylalanine; HVA = homovanillic acid.

*Significantly ($p < 0.05$) different from corresponding HC groups. (ANOVA followed by Newman-Keuls' test).

TABLE 3

CONCENTRATIONS (MEAN ± SEM ng/g) OF NE, 5-HT, AND THEIR METABOLITES IN THE MEDIAL FRONTAL CORTEX OF YOUNG (5 MONTH) AND OLD (22 MONTH) FEMALE F344 RATS

Group	*n*	NE	MHPG	MHPG/NE	5-HT	5-HIAA	5-HIAA/5HT
Young vehicle							
HC	19	445 ± 10	325 ± 23	0.73 ± 0.05	1040 ± 38	819 ± 29	0.81 ± 0.04
OF	20	407 ± 16	355 ± 21	0.88 ± 0.06†	1003 ± 60	898 ± 25	0.98 ± 0.08
Young *d*-FEN							
HC	19	433 ± 9	285 ± 14	0.66 ± 0.04	998 ± 34	819 ± 31	0.83 ± 0.03
OF	18	421 ± 11	293 ± 15	0.71 ± 0.04	955 ± 37	866 ± 25	0.93 ± 0.05
Old vehicle							
HC	8	420 ± 17	266 ± 16	0.63 ± 0.02	936 ± 31	870 ± 38	0.93 ± 0.06
OF	11	405 ± 12	236 ± 10	0.59 ± 0.03	931 ± 41	972 ± 45*	1.05 ± 0.05
Old *d*-FEN							
HC	11	404 ± 14	276 ± 21	0.69 ± 0.05	967 ± 55	944 ± 36	1.12 ± 0.09
OF	8	415 ± 10	239 ± 12	0.58 ± 0.02	926 ± 58	816 ± 41	0.91 ± 0.09

*Significantly ($p < 0.05$) different from young HC and Old *d*-FEN OF group.
†Significantly ($p < 0.05$) different from all other groups.

ACTH have previously been suggested as one possible mechanism underlying age-related increases in CORT secretion in males (28).

Whether age-related changes in gonadal steroids are responsible for the age-related differences between the sexes is not known. However, decreases in testosterone levels with age in males (17,29) and decreases in the phasic nature of estrogen secretion with age in females (23) suggests that these changes may be, in part, responsible.

In terms of PRL secretion, previous studies have demonstrated that basal PRL levels are elevated in the aging male and female rat (4,9,10,25). In this study we also detected an increase in basal levels of PRL with age. Interestingly, our data have shown that the PRL response to novelty stress, which is prominent in young male rats (15), is absent in young female rats but present in old female rats. The reasons behind the age specific PRL response of female rats to novelty stress remains undetermined. Earlier studies have demonstrated that young female rats are capable of responding to physical stressors such as restraint with a response equivalent to that of the male (19). The PRL response to mild psychological stressors has not been examined. The absence of a PRL response in young female rats may be stressor related, with young females not responding to novelty as a stressor. Certainly, based on the high activity and exploratory levels in the open field, young female rats show little fear or anxiety in this situation. Alternatively, it is possible that differences in circulating gonadal steroids could explain this phenomenon because both estrogen and androgen increase (13,14,18) PRL secretion in F344 rats. Changes in estrogen occurring with age would result in an increase in basal PRL secretion and could perhaps allow for the appearance of a PRL response to novelty.

Our previous studies have demonstrated that neurochemical changes occur in the MFC of male rats following novelty (22). Furthermore, NE turnover is influenced by age with old males showing a small increase in NE turnover in comparison to young (15,22). In the present study, we have demonstrated that in female rats, NE turnover rates are also influenced by age; however, the NE turnover rate response of old females was less than that of young females. This reduction in neurochemical turnover responses to novelty appears to be specific for NE because there were no age-related changes in DA or 5-HT turnover rates. In comparison to our previous study using male rats (15), female rats also appear to have greater levels of DA and DOPAC, and a greater DOPAC/DA ratio in the prefrontal cortex suggestive of increased DA turnover even under basal conditions. Unfortunately, because the tissues from males and females were not processed simultaneously, direct comparisons demonstrating sex differences are only speculative. However, this observation is consistent with previous reports of sex differences (females < males) in DA turnover in other brain regions such as the median eminence (11).

In order to address the question of a potential neurochemical involved in the age-related changes in hormonal and neurochemical stress responsiveness we administered the 5-HT releaser and uptake inhibitor *d*-FEN for a subchronic period of time. Our previous studies have shown that this regimen will alter some immune parameters (6) in young female rats and ameliorate some hormone secretory changes associated with age in male rats (15). Whether these previously reported effects of *d*-FEN are directly due to changes in 5-HT activity remain to be determined.

Consistent with previous studies, the present study documents the effects of subchronic *d*-FEN treatment on the pattern of hormone and neurochemical changes occuring following a psychological stressor in female rats. *d*-FEN was effective in attenuating the PRL response to novelty stress that was observed in old, but not young, rats. This effect of *d*-FEN on a hormonal response, which is augmented with age in females, is similar to the effect of *d*-FEN on the augmented ACTH and CORT response in aging male rats (15). Because there is no elevated ACTH and CORT response to novelty in aging female rats, an effect of *d*-FEN on the HPA axis would not be expected. Consistent with the hormonal findings, we have determined that 5-HT and DA turnover rates were not altered in old animals and *d*-FEN did not alter these turnover rates. *d*-FEN, however, did decrease NE turnover rate in response to novelty in young but not old female rats. The effect of *d*-FEN on open field NE turnover in young rats presumably is due to the absence of a NE turnover response in old females. This effect of *d*-FEN on NE systems is similar to that which we have previously reported for the aging male rat in that in male rats *d*-FEN treatment blocked the NE response to novelty in young and old animals.

With these data we have determined that age-related behav-

ioral, neuroendocrine, and neurochemical changes occur in female rats that are different from previously reported profiles in male rats. It remains to be shown whether there are inherent sex-specific aging responses or if these changes are a consequence of alterations in the gonadal steroid hormone milieu. In conclusion, *d*-FEN treatment seems to be beneficial in attenuating age-related hypersecretion of hormones in both the male [ACTH and CORT; (15)] and the female rat (PRL).

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