Pharmacology Biochemistry & Behavior, Vol. 16, pp. 73–79, 1982. Printed in the U.S.A.

Effect of Fusaric Acid on Aggression, Motor Activity, and Brain Monoamines in Mice

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Received 8 August 1980

DIRINGER, M. N., N. R. KRAMARCY, J. W. BROWN AND J. B. THURMOND. *Effect of fusaric acid on aggression, motor activity, and brain monoamines in mice.* PHARMAC. BIOCHEM. BEHAV. **16**(1) 73–79, 1982.—The effects of fusaric acid (FA), a dopamine-β-hydroxylase (DβH) inhibitor, were determined on aggression, motor activity, and brain monoamines at doses of 3.2 to 60 mg/kg following administration of dietary supplements of L-tyrosine or balanced protein to male albino mice. Compared to saline injected control animals, both aggression and motor activity were reduced by the highest doses of FA. Somewhat more reduction in aggression was observed in animals administered dietary supplements of casein compared to those given the tyrosine supplement. Treatment with FA at doses of 30 to 60 mg/kg decreased brain norepinephrine and dopamine, and decreased brain tyrosine in animals fed the tyrosine supplement. In contrast, FA increased 5-hydroxytryptamine, and caused marked increases in 5-hydroxyindoleacetic acid at the highest doses. The data suggest that the neurochemical effects of FA may not be the same in rats and mice.

Fusaric acid Dietary tyrosine Aggressive behavior Motor activity Dopamine-β-hydroxylase Norepinephrine Dopamine Serotonin

WHILE it is evident that central monoamines play a role in modulating aggression and arousal, the nature of their relationship remains elusive. Brain norepinephrine (NE) and dopamine (DA) activity have been postulated to be directly related to intraspecies aggression but inversely related to predatory aggression [3,32]. Intraspecies fighting among rats is induced by apomorphine [12], and among mice by L-DOPA at high doses or amphetamine at low doses [20], or by addition of tyrosine to the diet [41,42]. Barr *et al.* [4] observed that steady-state DA levels were higher in the hypothalamus of rats prone to fight other rats whereas NE and DA concentrations were similar in non-killer and killer rats engaging in muricide. These relationships are consistent with intraspecies fighting among mice in that higher hypothalamic DA concentrations have been found in aggressive mice when compared to non-aggressive animals [44].

In contrast, enhanced aggression is related apparently to diminished serotonergic (5-HT) function. Muricide [13, 14, 18, 27] and shock-induced fighting in rats [21,36] are facilitated by lesions or drug treatments which lower brain 5-HT. Maintaining rats on a tryptophan-free diet, which leads to depletion of brain 5-HT levels [14,22] induces muricide in nonkiller rats and facilitates muricide in killer rats which is reversed by restoring or raising brain 5-HT [14]. Mouse killing in rats induced by pharmacologic depletion of 5-HT is also reversed by restoring brain 5-HT [5, 13, 27].

Evidence also suggests that central catecholamine (CA) systems play a mediational role in behavioral arousal. Increased locomotor activity in rats has been reported following administration of amphetamine [35,43] and in mice following L-DOPA at low doses after pretreatment with reserpine [1] or PCPA [25], or following additions of tyrosine to the diet [6, 41, 42]. In contrast, administration of tryptophan [28] or 5-hydroxytryptophan [19] reportedly reduced motor activity in mice.

Establishing the nature of the modulatory effect of the central monoamines on animal aggression is an area of considerable complexity since most experimental models seem based on different interactions of these neurotransmitters [3,10]. A reciprocal relationship between CA and 5-HT functions was postulated by Mabry and Campbell [26] to account for aggressive behavior in mice. Hodge and Butcher [19,20] suggested that aggression is related to the potentiation of NE (and possibly DA) function and to the impairment of 5-HT function. Antelman and Caggiula [2] propose that NE neurons exert an indirect modulatory influence on DA systems and in this way regulate their function. When this modulatory influence is disrupted by activating or stressful stimuli (e.g., situations evoking aggressive behavior), behaviors critically dependent on normal DA function will be potentiated; under conditions of minimal stress, no change or perhaps a depression of DA-dependent behaviors may occur.

The purpose of the present investigation was to test these hypotheses by assessing the effects on aggression and motor activity of treatments intended to increase brain DA while

lowering brain NE. Hence, tyrosine was added to the diet to increase CA function and fusaric acid (FA), a dopamine-β-hydroxylase (DβH) inhibitor, was administered to decrease brain NE. Studies in rats have shown that treatments which raise brain tyrosine concentrations accelerate the rates at which CA neurons synthesize and turnover their transmitters [15, 16, 51]. Evidence from a number of sources [9, 24, 46, 49] suggests the possibility that brain NE biosynthesis may not only be regulated at the tyrosine hydroxylase step but at the DβH step as well. It has been shown in rats that brain DA increases whereas brain NE decreases following DβH inhibition with FA [17,48].

METHOD

Two experiments were conducted, the second being essentially a replication of the first.

Animals

Male mice of the CF-1 strain (Carworth Farms, Wilmington, MA), 11 weeks old, were housed five per cage. The laboratory was maintained at a temperature of 21°C, with a light cycle of 12 hr on, 12 hr off governed by three 100 W red bulbs superimposed for 12 hr with bright fluorescent lights. All procedures were performed during the first half of the dim portion of the cycle, between 12 noon and 5 p.m. The animals were marked with a spot of green liquid food dye for identification during testing.

Aggressive Behavior

A complete description of the apparatus used for producing and measuring territorial aggression has been published [40]. Briefly, the test animal (resident mouse) takes up lone residence for 24 hr in a 60 cm square box containing a 30 cm high tower in the center and has access through a 12 cm long tube to a standard mouse cage with food, water, and bedding. After this interval, a naive intruder mouse 13–15 weeks old is placed on the tower. Typically, the resident mouse intercepts and attacks the intruder within the first several minutes of the test, after the intruder climbs down the tower or by climbing the tower to reach the intruder. An attack was defined as a bout of activity lasting up to three seconds during which the resident bit the intruder at least once. The latency to the first attack was determined by recording with a stopwatch to the nearest second the time lapsed between placing the intruder on the tower and the first bite inflicted on the intruder by the resident. Most of the resident's aggression displayed toward the intruder takes place during the first 15 min of the test. The latency (in minutes) to first attack and the number of attacks over a 20-min observation period are used to quantify the level of aggression.

Motor Activity

In groups of five, an individual mouse was placed alone in one of five identical motimeters described by Knoll [23] and the accumulated activity for each mouse was recorded for 20 min. In this device the animal moves over aluminum contact plates mounted 4 mm apart in a clear 12 cm deep, 12 cm×40 cm rectangular Plexiglas box (testing cage) and a count is recorded for every passage between two plates.

Drugs

The dopamine-β-hydroxylase inhibitor (fusaric acid, U.S. Biochemical, Cleveland, OH) was dissolved in saline (0.9% NaCl) and the pH was adjusted to 6.0. The drug was freshly prepared before each IP injection and was given in a volume of 0.57 ml/100 g of mouse in doses of 15, 30, 45, and 60 mg/kg in Experiment 1 and 3.2, 15, 30, and 50 mg/kg in Experiment 2.

Diets

Mice were randomly designated as residents or intruders upon arrival at the laboratory, and residents were immediately given free access to water and a semi-synthetic basal diet (all diet materials were obtained from ICN Pharmaceuticals, Cleveland, OH) of the following composition: 12% casein protein, 5% corn oil, 70% corn starch, 2% cellulose, 4% Salt Mixture XIV, 2.2% Vitamin Diet Fortification Mixture, 4.8% dextrose. After maintenance on this diet for two weeks, the animals were randomly assigned to one of four groups (N=20 per group). In Experiment 1, two groups (A, B) remained on the 12% casein basal diet, a third group of animals (C) received a supplement of 4% casein to provide a total of 16% protein, and a fourth group (D) had the 12% casein diet supplemented with 4% tyrosine. Groups C and D were replicated in Experiment 2. The supplements replaced equal weights of dextrose; thus, all diets were isocaloric. The dietary materials for the resident mice were thoroughly mixed with enough water to make a batter, then oven-dried at 105°C for 40 min. The result was a cream-colored cake, which could be easily cut into pieces for purposes of feeding. Other mice, designated as intruders, were given free access to Rat/Mouse Purina Chow. The mice were weighed weekly to determine if any physical differences occurred as a result of the various dietary regimens.

Procedure

All four groups of mice were maintained on their respective diets for four weeks before drug administration was initiated. Groups B, C and D receiving injections of either FA or vehicle (0.9% saline) were tested three hours after an injection. Two doses each of FA and vehicle were administered in counterbalanced order, one injection to each animal every two weeks. Group A, which remained on unsupplemented 12% casein diet, was injected with vehicle and tested every two weeks, thus providing control data on the effects of repeated testing. Testing occurred every two weeks for ten weeks. Each round of testing for an animal consisted of a test of activity and aggression separated by 48 hr. Half of the test animals were assessed for aggression first and the other half for activity first to control for any confounding effects of test order. The order of testing for a particular animal remained constant throughout the experiment.

Biochemical Determinations

Separate groups of animals (N=5 per group), maintained for four weeks on the semi-synthetic diets, were killed by cervical dislocation, their brains removed, and immediately homogenized in ten volumes of cold acidified n-butanol. Serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), DA and NE in whole brain were determined spectrophotofluorometrically according to the method of Cox and Perhach [8] and Chang [7]. Tyrosine (TYR) was analyzed according to Wong *et al.* [50] as modified by Phillips [31]. Monoamine (2 μg/ml) and tyrosine (250 μg/ml) standards were shaken briefly with 2.5 ml acidified n-butanol, then carried through the entire procedure. External standards were also prepared and run with each set of samples to obtain a measure of recovery. A pooled sample was generated from the super-

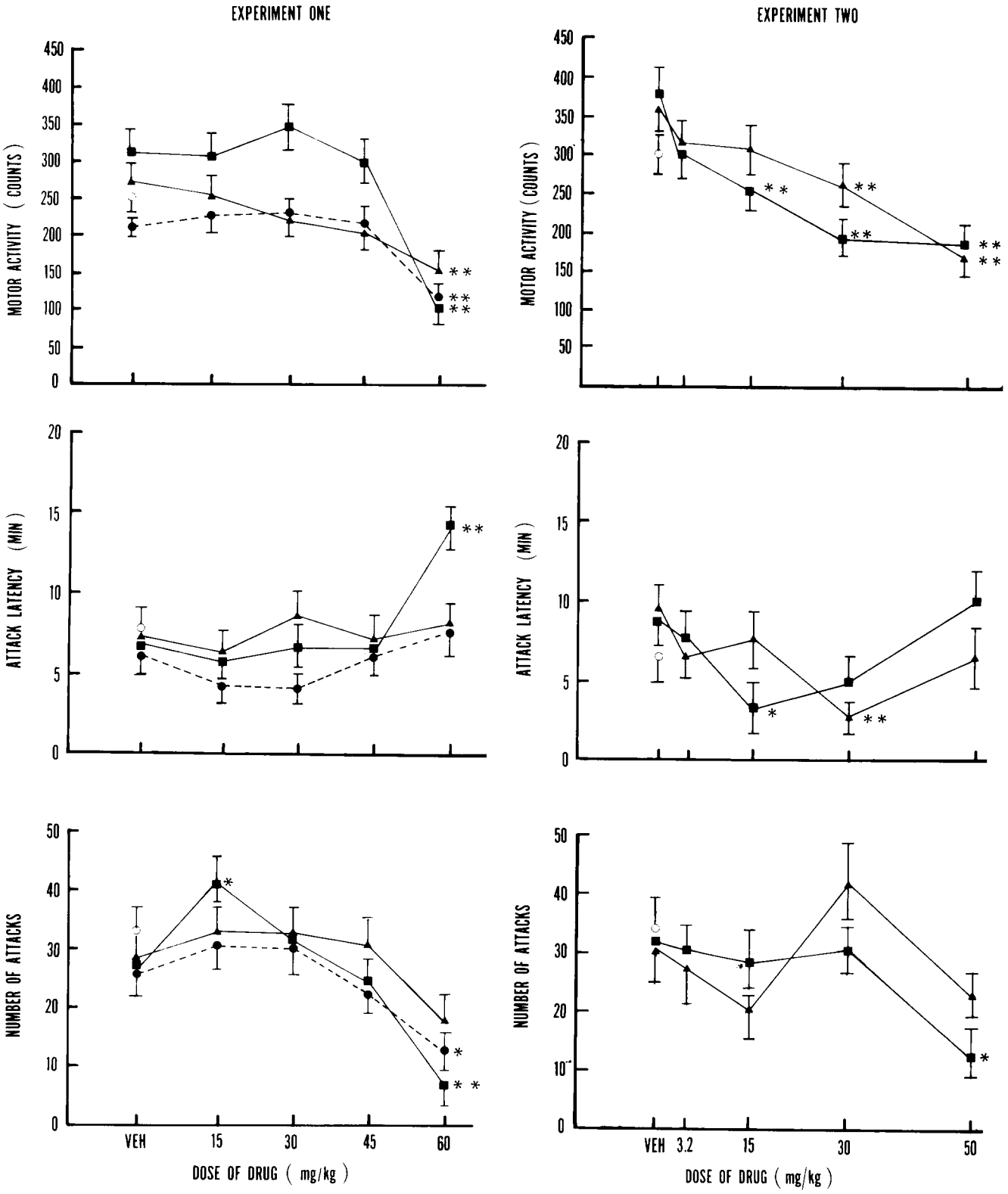

FIG. 1. Effect of fusaric acid plus unsupplemented 12% casein diet (solid circles), plus 4% casein supplement (solid squares), or plus 4% L-tyrosine supplement (solid triangles) on the motor activity, attack latency, and number of attacks by test mice on intruders. Effect of repeated saline injections on 12% casein condition is shown above the VEH point (open circle). All injections were IP. Results are given as mean with SEM of 20 determinations. Statistical significance show differences from the VEH value for a given condition. *$p<0.05$, **$p<0.01$.

natants of the individual brains and carried through the procedure as a tissue blank. Recovery of each substance ranged from 65 to 90 per cent.

Statistics

A two-factor (diet and drug) analysis of variance (ANOVA) with repeated observations on one factor (drug) was conducted on the behavioral data, followed where significant by Dunnett's test for comparing individual treatment means with the control group mean. Interactions were analyzed using analysis of variance for the simple effects of the drug doses for each category of diet according to Winer [47]. Based on tests of homogeneity of variance and of the distributions about the means, parametric statistics were deemed appropriate for the data, particularly in view of the characteristic robustness of the analysis of variance [47]. Similar analyses for independent observations were applied to the neurochemical data.

RESULTS

Weight Gain

The mice in each diet supplement group gained approximately the same amount of weight over the 15-week period of maintenance on the diets. The mean weights for animals maintained on the basal 12% casein diet, the 4% tyrosine supplement, and the 4% casein supplement were respectively, 35, 33, and 36 g before supplementation, 43, 41, and 42 g after twelve weeks on the diet. The weight gain of the mice on each of these diets was the same. This agrees with prior data on weight gain in our laboratory in which mice were fed essentially identical supplements [42] and with more extensive data on weight gain [41] in which mice fed identical supplements gained the same amount of weight as animals fed Rat/Mouse Purina Laboratory Chow.

Motor Activity

Although the difference in motor activity of animals in Experiment 1 maintained on supplements of 4% casein or 4% tyrosine was not significant, $F(1,38)=2.85$, $p=0.90$, the administration of FA produced effects in each of these groups (Fig. 1). The ANOVA for repeated measures showed a highly significant drug effect on motor activity, $F(4,152)=20.48$, $p<0.001$, and a significant diet×drug interaction, $F(4,152)=4.38$, $p<0.01$. Figure 1 (left panel) shows that the highest dose of FA (60 mg/kg) decreased motor activity significantly in all three diet groups. The relatively larger drop of the casein supplemented group was the main source of the significant interaction, $F(4,152)=12.60$, $p<0.001$. Administration of FA in Experiment 2 (Fig. 1, right panel) reduced motor activity in both diet groups, $F(4,152)=18.92$, $p<0.01$. No differences due to diet or diet×drug interaction were obtained.

Aggression

The effects of diet supplementation and FA on attack latency in Experiment 1 are summarized in Fig. 1 (left panel). No effects on attack latency due to diet were shown by the ANOVA but a significant drug effect, $F(4,152)=7.23$, $p<0.001$, and a diet×drug interaction, $F(4,152)=3.51$, $p<0.01$, were obtained. The significant interaction was due mainly to the relatively large increase in attack latency in the casein supplemented group at the 60 mg/kg dose of FA, $F(4,152)=3.90$, $p<0.01$. A comparison of mice in this group with saline injected controls was significant, Dunnett's $t(152)=4.24$, $p<0.01$.

Diet had no significant effects on number of attacks (Fig. 1) but again the drug effect was highly significant, $F(4,152)=12.68$, $p<0.01$. The number of attacks was increased only in the casein group as compared to their vehicle injected control value and only at the lowest dose of FA, Dunnett's $t(152)=2.70$, $p<0.05$. The highest dose of FA decreased this measure significantly in the casein supplemented group compared to the vehicle injected control value, Dunnett's $t(152)=3.85$, $p<0.01$. A similar decrease at 60 mg/kg by FA in the tyrosine supplemented group did not reach statistical significance.

The effect of FA on attack latency in Experiment 2 (Fig. 1, right panel) was significant, $F(4,152)=3.98$, $p<0.01$, resulting in reductions of attack latency at the 15 mg/kg dose for animals fed additional casein, Dunnett's $t(152)=2.65$, $p<0.05$, and at 30 mg/kg for those fed additional tyrosine, Dunnett's $t(152)=3.14$, $p<0.01$. The ANOVA yielded no significant effects on latency to attack due to diet or diet×drug interaction. Administration of FA significantly decreased the number of attacks, $F(4,152)=3.33$, $p<0.05$, apparently due mainly to the sharp drop in attacks in the casein group at 50 mg/kg (Fig. 1, right panel). The number of attacks was decreased significantly at this point compared to the vehicle injected control value, Dunnett's $t(152)=2.41$, $p<0.05$. The tyrosine supplemented group displayed an increase in attacks at the 30 mg/kg dose but this did not reach statistical significance compared to the saline injected control value.

Neurochemical Parameters

Table 1 summarizes biochemical data from analyses of mouse brains of animals treated identically to those used for behavioral testing, except that no behavioral tests on these mice were conducted. The data were analyzed with use of ANOVA in which the two independent variables (diet, drug) were manipulated and five dependent measures (NE, DA, 5-HT, 5-HIAA, and TYR) were analyzed. These analyses were followed by tests (Dunnett's t) for comparing individual treatment means with the control group mean (see Table 1).

Significant biochemical differences between the three diets were determined by applying a simple ANOVA to the control values, followed where significant by Dunnett's test. Significant differences were obtained between the diets for 5-HIAA in Experiment 1, $F(2,12)=3.90$, $p<0.05$, and for TYR in Experiment 1, $F(2,12)=87.52$, $p<0.001$, and in Experiment 2, $F(2,12)=11.27$, $p<0.001$. Adding 4% casein to the 12% casein diet produced no significant biochemical differences. However, the addition of 4% tyrosine reduced 5-HIAA in Experiment 1, Dunnett's $t(12)=2.71$, $p<0.05$, and raised levels of brain tyrosine in both experiments, Dunnett's $t=11.91$ and 4.13 in Experiments 1 and 2, respectively; $df=12$; $p<0.001$ in each case.

In Experiment 1 significant effects were obtained on NE due to drug, $F(2,24)=7.48$, $p<0.01$, DA due to drug, $F(2,24)=9.57$, $p<0.001$, 5-HT due to diet, $F(1,24)=6.8$, $p<0.05$, drug, $F(2,24)=7.02$, $p<0.01$, and diet×drug interaction, $F(2,24)=3.92$, $p<0.05$, 5-HIAA due to drug, $F(2,24)=10.89$, $p<0.001$, TYR due to diet, $F(1,24)=86.84$, $p<0.001$, drug, $F(2,24)=26.1$, $p<0.001$, and diet×drug interaction, $F(2,24)=5.90$, $p<0.01$.

It is apparent from the data of Table 1 that decreased

TABLE 1

EFFECTS OF DIET SUPPLEMENT AND FUSARIC ACID (FA) ON CONCENTRATIONS OF NOREPINEPHRINE (NE), DOPAMINE (DA), SEROTONIN (5-HT), 5-HYDROXYINDOLEACETIC ACID (5-HIAA), AND TYROSINE (TYR) IN MOUSE BRAIN

	NE	DA	5-HT	5-HIAA	TYR
Experiment 1 Treatment					
12% Casein (control)	0.54 ± 0.03	1.14 ± 0.13	0.54 ± 0.03	0.79 ± 0.05	13.48 ± 1.25
Plus 4% Casein + Saline	0.56 ± 0.07	1.59 ± 0.36	0.62 ± 0.02	0.67 ± 0.03	16.07 ± 1.60
+ 15 mg/kg FA	0.46 ± 0.07	1.44 ± 0.21	0.71 ± 0.02†	0.70 ± 0.04	8.13 ± 1.37
+ 60 mg/kg FA	0.35 ± 0.02†	0.79 ± 0.11*	0.58 ± 0.03	1.58 ± 0.16‡	7.35 ± 0.58*
Plus 4% Tyrosine + saline	0.55 ± 0.02	1.70 ± 0.34	0.49 ± 0.02	0.62 ± 0.05	46.15 ± 2.68
+ 15 mg/kg FA	0.49 ± 0.02	1.71 ± 0.18	0.62 ± 0.04†	0.66 ± 0.02	36.29 ± 5.40*
+ 60 mg/kg FA	0.38 ± 0.06*	0.84 ± 0.07*	0.61 ± 0.04*	1.21 ± 0.08‡	17.96 ± 3.09‡
Experiment 2 Treatment					
12% Casein (control)	0.58 ± 0.01	1.63 ± 0.30	—	0.69 ± 0.04	9.55 ± 1.30
Plus 4% Casein + saline	0.57 ± 0.03	1.61 ± 0.34	—	0.71 ± 0.04	9.88 ± 0.95
+ 1.6 mg/kg FA	0.52 ± 0.03	1.59 ± 0.35	—	0.66 ± 0.05	10.87 ± 1.37
+ 3.2 mg/kg FA	0.44 ± 0.05	1.51 ± 0.29	—	0.65 ± 0.04	7.86 ± 0.69
+ 15 mg/kg FA	0.43 ± 0.05	1.40 ± 0.25	—	0.74 ± 0.05	7.18 ± 0.41
+ 30 mg/kg FA	0.34 ± 0.02‡	0.79 ± 0.06*	—	0.72 ± 0.03	6.14 ± 0.29
+ 50 mg/kg FA	0.37 ± 0.03†	0.77 ± 0.10*	—	1.42 ± 0.08‡	7.61 ± 0.68
Plus 4% tyrosine + saline	0.56 ± 0.06	1.69 ± 0.37	—	0.60 ± 0.05	35.14 ± 7.4
+ 1.6 mg/kg FA	0.55 ± 0.07	1.41 ± 0.28	—	0.77 ± 0.20	27.71 ± 4.33
+ 3.2 mg/kg FA	0.55 ± 0.06	1.31 ± 0.15	—	0.64 ± 0.06	24.97 ± 0.58*
+ 15 mg/kg FA	0.49 ± 0.04	1.48 ± 0.17	—	0.68 ± 0.04	22.64 ± 2.51†
+ 30 mg/kg FA	0.31 ± 0.02‡	0.74 ± 0.08*	—	0.67 ± 0.03	14.79 ± 1.31‡
+ 50 mg/kg FA	0.35 ± 0.07†	0.80 ± 0.08*	—	1.15 ± 0.07‡	16.09 ± 2.17‡

Results are given as mean μg/g wet weight ± SEM (N=5 for each determination). Treatment means in each diet condition were compared with the matched saline-injected dietary control (Dunnett's t).

*$p<0.05$.

†$p<0.01$.

‡$p<0.005$.

levels of brain NE and DA are associated with a decrease in brain tyrosine following FA treatment, especially in the tyrosine supplemented conditions. The source of the diet×drug interaction for TYR is due to the marked dose-related decrease in brain tyrosine following FA treatment in the tyrosine supplemented animals, $F(2,24)=23.34, p<0.001$, compared to the moderate decreases for those given casein. In both diet conditions, 5-HIAA was increased significantly by the highest dose of FA (60 mg/kg). Animals receiving the tyrosine supplement evidenced a very large increase in TYR. FA reduced brain TYR in a dose-related manner for the tyrosine supplemented animals. Thus, FA depleted brain tyrosine most in the tyrosine-supplemented mice, but tyrosine loading did maintain normal (untreated, casein diet) levels of tyrosine (even then, there was a behavioral effect).

The biochemical data for Experiment 2 were analyzed with use of ANOVA as in Experiment 1. The ANOVA indicated significant effects on NE due to drug, $F(5,48)=8.15$, $p<0.01$, DA due to drug, $F(5,48)=5.21, p<0.01$, 5-HIAA due to drug, $F(5,48)=21.22$, $p<0.01$, TYR due to diet, $F(1,48)=93.07$, $p<0.01$, drug, $F(5,48)=5.42$, $p<0.01$, and diet×drug interaction, $F(5,48)=2.59$, $p<0.05$.

The highest doses of FA (30 and 50 mg/kg) decreased brain NE and DA significantly in both diet groups. In the tyrosine supplemented animals these decreased levels are associated apparently with reduced concentrations of brain tyrosine following FA treatment. The source of the diet×drug interaction for TYR is due to the more than two-fold drop in brain tyrosine as a function of FA treatment in the tyrosine supplemented animals as opposed to the lesser (and nonsignificant) effects of FA in the casein fed animals, $F(5,48)=7.60$, $p<0.01$.

DISCUSSION

Dietary tyrosine and FA were administered to mice in the present study, not because tyrosine loads would be expected to alter the action of FA, but rather because tyrosine administration has been shown to increase brain CA metabolism [15, 16, 51] and FA, a DβH inhibitor, has been shown to reduce brain NE [30,48]. The effect of these joint manipulations should therefore have been to increase brain DA function and decrease brain NE, and thereby permit a test of the hypothesized results on behaviors supposedly mediated by central DA systems. In view of prior findings with mice and rats associating increases in aggression with enhanced DA function [4, 12, 25, 44], and in rats following DβH inhibition [34], the combined treatment of tyrosine and FA would be expected to enhance aggression. In contrast, DβH inhibition in mice reportedly reduces aggression [20, 33, 38, 39] and locomotor activity [20,29]. The effects of dietary tyrosine and FA in the present study seem consistent with the data of these prior studies, taken as a whole. Administration of FA caused reductions in aggressive behavior and motor activity

at the highest doses used (50–60 mg/kg), with decreases in aggression being less severe in the tyrosine supplemented mice. It should be noted that because of the decreases in motor activity, the decreases in aggression may be non-specific.

In an earlier study [41] we observed that a tyrosine supplement increased aggressive behavior after one week, but an apparent tolerance developed to this effect after five weeks [42]. In the present study, the animals were fed the dietary supplements for four weeks before behavioral testing began; moreover, testing took place over a ten-week period while the animals were maintained on the diet. It seems reasonable to suppose that the conditions of the present study produced a similar tolerance to the effects of tyrosine. The application of adrenergic agonists to tissues frequently results in a subsensitive response to the subsequent addition of agonists [45].

Although prior *in vivo* studies with rats have not reported a decrease in brain DA following FA treatment [48], the reduction in aggression and motor activity observed here and in prior studies with mice after DβH inhibition [20, 33, 39] is consistent with the low brain NE and DA obtained following FA treatment in the present study. The most unexpected and consistent finding in the present experiments was that FA reduced brain tyrosine in a dose-dependent manner. This was evidenced most dramatically by the groups on tyrosine-supplemented diets. Here, brain tyrosine levels in non-treated animals were 3–4 times control levels, yet FA at higher concentrations reduced these levels by half. These same concentrations of FA reduced brain tyrosine concentrations in casein-supplemented animals to 50–60 percent of control values. Although one can only speculate as to the reason for this effect, it is consistent with another finding of these experiments, that FA not only reduces NE (as expected), it also reduces DA. If FA were acting only on the β hydroxylase, and the supply of CA precursor were adequate, one might expect DA to increase, not decrease. However, by reducing the concentration of the amino acid precursor of both monoamines, FA should have the effect observed.

Slight increases in 5-HT and marked increases in 5-HIAA were observed in mouse brain following FA at 50 and 60 mg/kg in both the casein and tyrosine supplemented groups. Using another DβH inhibitor, Fukumori *et al.* [11] found that treatment with disulfiram increased 5-HT and 5-HIAA in rat brain. The significant increases in 5-HIAA which we observed at the highest dose of FA in both diet conditions may be taken to indicate, as others have reported [37], enhanced metabolism of 5-HT.

In summary, we have investigated the interaction of FA (a DβH inhibitor) pretreatment, and tyrosine or casein supplementation on motor activity, attack latency and attack frequency in mice fed a semi-synthetic basal diet in an attempt to determine the relative roles of central NE and DA in these behaviors. A decrease in brain DA as well as NE was observed following FA treatment which was associated with reduced levels of brain tyrosine. Although this finding was unexpected, it was noted that it is consistent with decreased levels of aggression and motor activity following DβH inhibition reported here and elsewhere.

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