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Functional and Biochemical Evidence for Altered Serotonergic Function in the Fawn-Hooded Rat Strain

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AULAKH, C. S., T. TOLLIVER, K. M. WOZNIAK, J. L. HILL AND D. L. MURPHY. *Functional and biochemical evidence for altered serotonergic function in the Fawn-Hooded rat strain.* PHARMACOL BIOCHEM BEHAV **49**(3) 615–620, 1994. – Administration of various doses of DOI (a 5-HT_{2A}/5-HT_{2C} agonist) produced hyperthermia that was significantly less in the FH rat strain relative to the Wistar rat strain. Similarly, administration of various doses of ipsapirone (a 5-HT_{1A} agonist) produced hypothermia that was significantly less in the FH rat strain relative to the Wistar rat strain. Furthermore, m-CPP (a 5-HT agonist)-induced increases in growth hormone levels were also significantly less in the FH rat strain relative to the Wistar rat strain. There was no significant difference in the levels of either 5-HT or 5-HIAA between the two rat strains in the frontal cortex, hippocampus, hypothalamus, and striatum. In the brain stem, however, both 5-HT and 5-HIAA levels were significantly lower in the FH rat strain relative to the Wistar rat strain. On the other hand, 5-HT turnover rate was significantly higher in the hypothalamus and striatum and significantly lower in the hippocampus in the FH rat strain relative to the Wistar rat strain. These findings provide further evidence for altered serotonergic function in the FH rat strain and, in addition, suggest that the FH rat strain may prove to be a useful genetic model for some neuropsychiatric disorders with possible abnormalities in serotonergic function such as depression, obsessive-compulsive disorder, and the eating disorders.

m-CPP DOI Ipsapirone Rectal temperature Growth hormone Genetic model Depression Subsensitive

THE FAWN-HOODED (FH) rat strain is associated with a hemorrhagic disorder known as platelet storage pool deficiency, a genetic disorder analogous to that in the Chediak-Higashi syndrome of humans (26,30). The blood platelets from FH rats have decreased numbers and contents of dense granules and decreased concentrations of serotonin (35). Some reports have suggested either absence (10) or diminished (3) ^{3}H-imipramine binding sites on platelets and in brain tissue of FH rats, although these findings have been disputed (19,27). Whole brain serotonin concentrations were not found to be significantly different between FH and Sprague–Dawley (SD) rats (20).

In several previous reports from this laboratory, we have demonstrated that FH rats are functionally subsensitive to a) the food intake suppressant effects of 5-HT agonists such as m-chlorophenylpiperazine (m-CPP), 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OHDPAT), and fenfluramine in a food-deprived paradigm (36), b) the hyperphagic effects of 5-HT_{1A} agonists (8-OHDPAT and buspirone) in a free-feeding paradigm, c) the locomotor suppressant effects of m-CPP (5), and (d) m-CPP-induced increases in plasma prolactin (6) relative to Wistar and SD rat strains. Other investigators have also demonstrated altered responses to serotonin agonists in FH rats relative to SD rats (14). Recently, we demonstrated functional subsensitivity of 5-HT_{2C} or α_2-adrenergic heteroreceptors mediating clonidine-induced growth hormone release in the FH rat strain relative to the Wistar rat strain (4).

The purpose of the present study was to extend these observations to other paradigms and, also, to investigate possible biochemical mechanisms involved in these defects. Therefore,

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we compared the effects of various doses of ipsapirone (a 5-HT_{1A} agonist) and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, a 5-HT_{2C}/5-HT_{2A} agonist) on rectal temperature and of m-CPP (a 5-HT agonist) on growth hormone (GH) levels in FH and Wistar rats. Furthermore, we measured baseline concentrations of serotonin (5-HT), its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and 5-HT turnover in various brain areas in FH and Wistar rats.

METHOD

Male rats of the Wistar and FH strains, weighing approximately 250 g, were used. They were housed six per cage in a temperature controlled (24 ± 1°C) room with a 12 L : 12 D cycle (lights on at 0700 h). The animals had free access to Purina rat chow and water at all times. Separate groups of animals were used for studying levels of serotonin and its metabolite, 5-HT turnover and for each dose of the 5-HT agonists in both the neuroendocrine and temperature studies.

Temperature Studies

Forty-eight animals (six animals from each strain at each dose of DOI or ipsapirone) were used. Animals were brought into the test environment (22 ± 1°C) at least 1 h prior to any recording. Rectal temperature was measured with a rectal probe and digital thermometer (Sensorterk Inc., Clifton, NJ), all recordings being made between 1000 and 1400 h. Each animal received six habituating exposures to the rectal probe, which was inserted 2.5 cm into the colon, while each rat was held lightly by the tail. Rectal temperature was recorded prior to and 30, 60, and 90 min after intraperitoneal (IP) injection of various doses of DOI or ipsapirone.

Neuroendocrine Studies

Forty-eight animals (six animals from each strain at each dose of the drug) were used. Saline or various doses of m-CPP were injected IP between 1030 and 1100 h. Two separate experiments were performed on 2 separate days. In the first experiment, the rats received saline or the lowest dose (1.25 mg/kg) of m-CPP. In the second experiment, the rats received either 2.5 or 5.0 mg/kg dose of m-CPP. In the first experiment, the Wistar animals were injected and sacrificed first followed by FH animals at each dose of the drug. In the second experiment, the FH animals were injected and sacrificed first followed by Wistar animals at each dose of the drug.

The rats were sacrificed by decapitation, and trunk blood was collected in centrifuge tubes containing 0.5 ml of ethylenediamine-tetraacetic acid. Following centrifugation, plasma samples were collected and stored at −80°C. The plasma concentrations of GH were measured by radioimmunoassay as described elsewhere (11).

Biochemical Studies

Twelve animals (six animals from each strain) were sacrificed by decapitation and the different brain areas were dissected out. The concentrations of 5-HT and its metabolite 5-HIAA were determined by high pressure liquid chromatography (HPLC) according to the method described by Mefford (24) with little modification. In brief, frozen tissue samples were weighed and transferred to 1.5 ml Eppendorf tubes containing 150 ml 0.1 N perchloric acid and 50 ml 10^{-6} M *N*-methylserotonin. Samples were sonicated on ice briefly using a Heat Systems ultrasonic model W-300 sonicator fitted with a microtip at a setting of 3. The mixture was then centrifuged at 12,000 × *g* for 2 min and the clear supernate was removed. A 50 μl aliquot of the supernate was applied to a C-18 Axxion column, 15 × 0.45 cm, using a Gilson model 231/401 sample injector (Thomson Instrument Co., Springfield, VA) fitted with a 50 μl loop. Solvent was delivered at a constant flow rate of 0.6 ml/min by a LKB model 2150 HPLC pump. The mobile phase was 0.2 M citric acid, 100 mg/l EDTA, 450 mg/l octane sulfonic acid, 5 ml/l triethylamine, and 6.5% acetronitrile. Detection was accomplished amperometrically using the model LC4B amperometric detector (Bioanalytical Systems, West Lafayette, IN) with a dual glassy working electrode at a applied potential of 0.85 V vs. a Ag/AgCl reference. Chromatographs were recorded on a Kipp and Zonen dual pen strip chart recorder.

For the 5-HT turnover study, 48 animals (six animals from each strain at each time point) were used. Turnover rates of 5-HT were estimated on the basis of the increases in brain 5-HT concentrations that followed inhibition of monoamine oxidase after IP administration of pargyline (75 mg/kg) as previously described (34). The rats were killed by decapitation at different time points (0, 15, 30, and 60 min), and the different brain areas were dissected out. The concentrations of 5-HT were determined by HPLC as described above.

Drugs

The drugs, DOI HCl, pargyline HCl (Research Biochemicals, Inc., Natick, MA) m-CPP HCl (Aldrich Chemical, WI), and ipsapirone HCl (Bristol Myers Co., IN) were used in the study. All drugs were dissolved in 0.9% saline. The volume injected was 0.1 ml/100 g of body weight. All drug doses given in the text refer to the salt.

Data Analysis

GH data were examined using a two-way analysis of variance testing for strain, dose, and strain × dose effects accompanied by Bonferroni-corrected *t*-tests comparing the two strains at each dose. The data used in these analyses were the $\log_{10}$ of the GH level to adjust for heterogeneous variances in the raw GH data. Changes in body temperature caused by DOI and ipsapirone were each examined using a two-way repeated measures design analysis of variance in which strain was the between-subjects effect and time the within-subjects effect. These analyses were accompanied by contrasts specified a priori of the changes in temperature from baseline values at each time attributable to strain and dose effects. The levels of 5-HT and 5-HIAA in five brain regions were simultaneously compared in the two rat strains using a multivariate analysis of variance. The significant multivariate strain/region interaction was further explored for each neurotransmitter by comparing the two strains within each region with an analysis of variance. Turnover rates of 5-HT in the five brain regions of the two strains were compared using two tailed *t*-tests.

RESULTS

Administration of various doses of DOI produced hyperthermia (Fig. 1). Analysis of variance showed a significant, $F(3, 57) = 18.33$, $p < 0.001$, time × strain interaction. Further analysis revealed that increases in rectal temperature following administration of 1.0 and 2.5 mg/kg doses of DOI were significantly ($p < 0.001$) less in the FH rats relative to the Wistar rats at 30, 60, and 90 min (Fig. 1).

Administration of various doses of ipsapirone produced

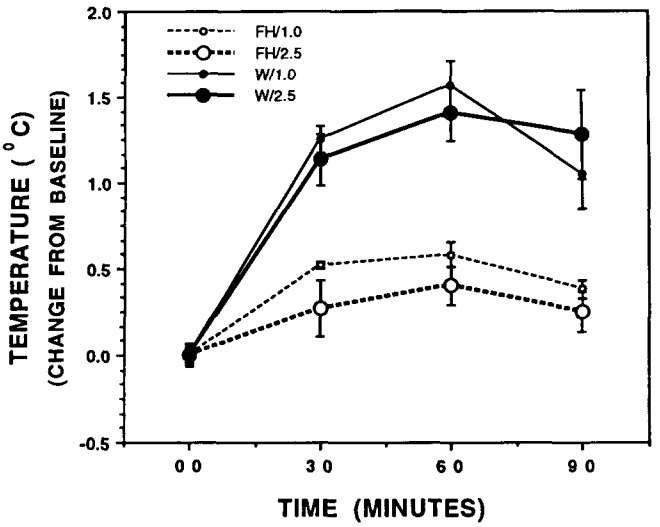

FIG. 1. Effects of various doses of DOI on rectal temperature in the Wistar and Fawn-Hood rat strains. Values are expressed as means ± SEM from six animals. Increases in rectal temperature were significantly ($p < 0.001$) less in FH rats relative to Wistar rats at 30, 60, and 90 min following administration of 1.0 and 2.5 mg/kg doses of DOI.

hypothermia (Fig. 2). Analysis of variance showed a significant, $F(1, 20) = 17.33$, $p < 0.001$, strain × dose interaction as well as a significant, $F(3, 60) = 6.95$, $p < 0.01$, time × strain interaction. Further analysis revealed that only the effect of the high dose (2.5 mg/kg) of ipsapirone was significantly attenuated in the FH rats relative to the Wistar rats at 30, 60, and 90 min (Fig. 2).

Administration of various doses of m-CPP produced increases in GH levels (Fig. 3). Analysis of variance showed a significant, $F(1, 28) = 14.52$, $p < 0.001$, strain effect. Further analysis revealed that the GH increases were significantly less in the FH rats relative to the Wistar rats following 2.5 and 5.0 mg/kg doses of m-CPP (Fig. 3).

The baseline concentrations of 5-HT and 5-HIAA in various brain areas in the two rat strains are shown in Fig. 4. There was no significant difference in the levels of either 5-HT or 5-HIAA between the two rat strains in the frontal cortex, hippocampus, hypothalamus, and striatum. In the brain stem, however, 5-HT, $F(1, 10) = 12,18$, $p < 0.01$, as well as 5-HIAA, $F(1, 10) = 7.79$, $p < 0.05$, levels were significantly less in the FH rats relative to the Wistar rats.

The turnover rates of 5-HT in different brain areas in FH and Wistar rats are shown in Table 1. 5-HT turnover rate was significantly higher in the hypothalamus and striatum and significantly lower in the hippocampus in the FH rats relative to the Wistar rats (Table 1).

DISCUSSION

The present study demonstrates that systemic administration of DOI induces hyperthermia in rats. Our results are consistent with a previous report using SD rats (29). In recent years, DOI and another phenylisopropylamine (+)-1-(2,5-dimethoxy-4-bromophenyl-2-aminopropane (DOB), have been radioactively tagged and have been used to biochemically characterize the 5-HT_{2A} receptors (2,12). However, these phenylisopropylamine hallucinogens also compete strongly for [^{3}H] mesulergine-labeled 5-HT_{2C} receptors in homogenate binding assays, with a similar rank order of potency at [^{3}H]-DOB-labeled 5-HT_{2A} receptors (33). However, 5-HT_{2A} receptor-mediated responses such as quipazine-induced wet dog shakes and 5-MeODMT-induced hyperthermia have been reported to be accentuated in the FH rat strain relative to the SD rat strain (14). On the other hand, 5-HT_{2C} receptor-mediated responses such as m-CPP-induced increases in plasma prolactin (6), decreases in food intake (36), and locomotor activity

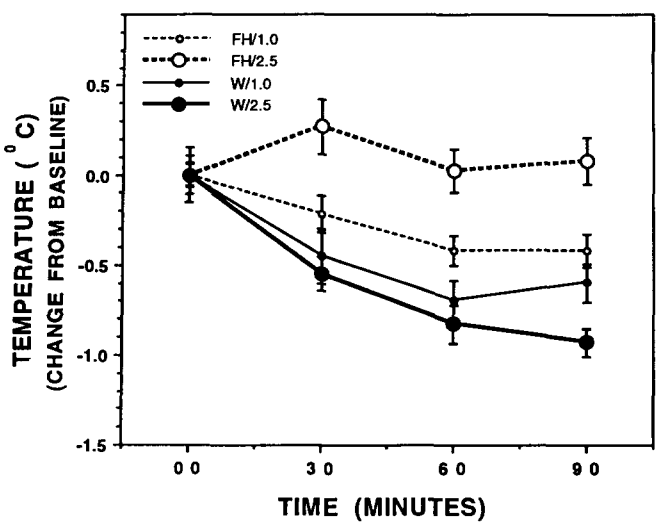

FIG. 2. Effects of various doses of ipsapirone on rectal temperature in the Wistar and Fawn-Hooded rat strains. Values are expressed as means ± SEM from six animals. Decreases in rectal temperature were significantly ($p < 0.01$) less in FH rats relative to Wistar rats at 30, at 60, and 90 min following administration of 2.5 mg/kg dose of ipsapirone.

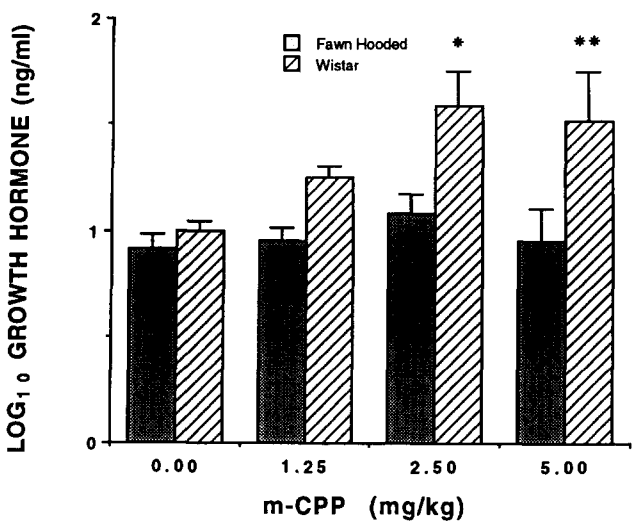

FIG. 3. Effects of various doses of m-CPP on plasma growth hormone levels in the Wistar and Fawn-Hooded rat strains. Values are expressed as means ± SEM from six animals. Values of Wistar animals significantly different from Fawn-Hooded animals are represented by $*p < 0.05$; $**p < 0.01$.

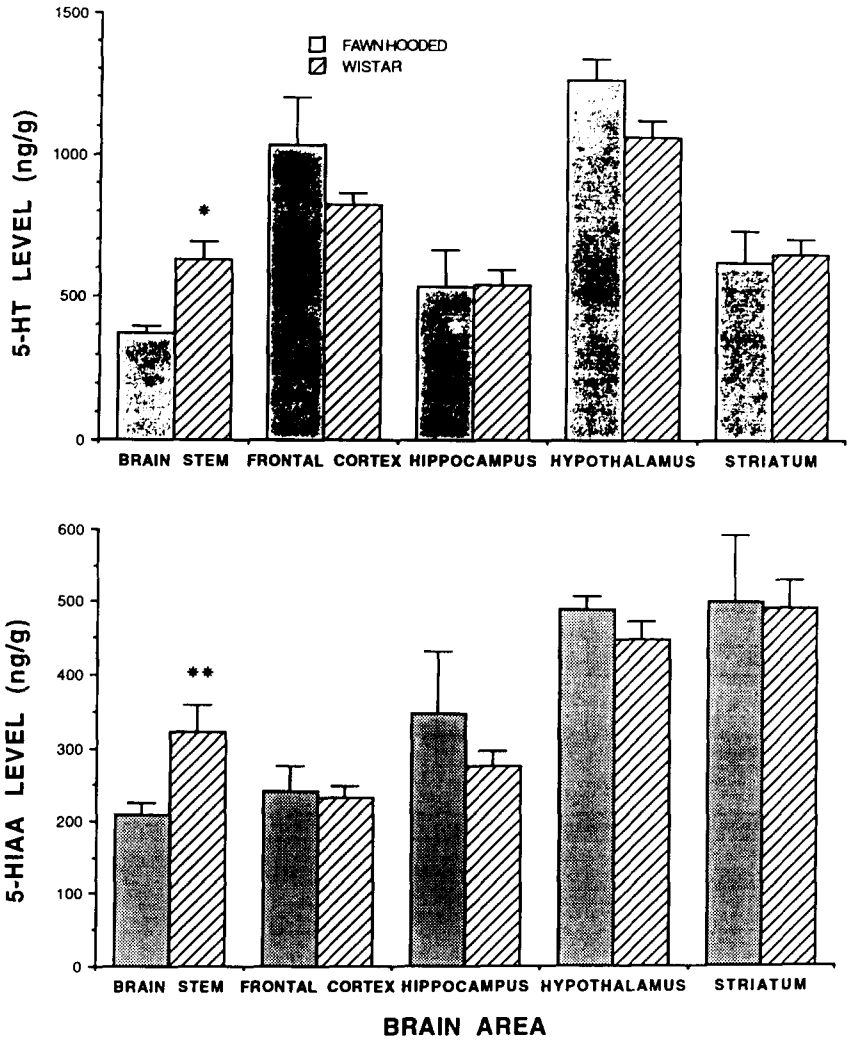

FIG. 4. Baseline levels of 5-HT and 5-HIAA in various brain areas in the Wistar and Fawn-Hooded rat strains. Values are expressed as means ± SEM from six animals. Values of Wistar animals significantly different from Fawn-Hooded animals are represented by $*p < 0.05$; $**p < 0.01$.

(5) have been reported to be attenuated in the FH rat strain relative to Wistar and SD rat strains. In two recent reports, we have demonstrated B_{max} values for 5-HT_{2A} receptors labeled by [^{3}H]-ketanserin to be significantly higher in the striatum and the frontal cortex of the FH rats compared to SD rats (16) while B_{max} values for 5-HT_{2C} receptors labeled by [^{3}H] mesulergine to be significantly lower in the hippocampus of the FH rats compared to Sprague–Dawley rats (17). Because DOI-induced hyperthermia was significantly less in the FH rat strain relative to the Wistar rat strain in the present study, it is tempting to speculate that 5-HT_{2C} receptors may mediate DOI-induced hyperthermia. However, caution must be taken because the pharmacological relation of 5-HT_{2C} to 5-HT_{2A} receptors is undefined at present and remains an important area for further investigation.

In the present study, systemic administration of ipsapirone produced hypothermia, which is consistent with previous findings that the selective 5-HT_{1A} agonist 8-OHDPAT induces hy-

TABLE 1

5-HT TURNOVER RATES IN DIFFERENT BRAIN AREAS IN FAWN-HOODED AND WISTAR RATS

	5-HT Turnover Rates*	
Brain Region	Fawn-Hooded (μg/g/h)	Wistar (μg/g/h)
Striatum	0.766 ± 0.117†	0.353 ± 0.036
Brain Stem	1.235 ± 0.050	1.316 ± 0.021
Frontal Cortex	0.684 ± 0.207	0.621 ± 0.049
Hippocampus	0.189 ± 0.026†	0.306 ± 0.039
Hypothalamus	1.464 ± 0.104†	1.039 ± 0.087

*Turnover rates, expressed as the mean ± SEM, were calculated as described in the Method section.

†$p < 0.05$.

pothermia in rodents (14,37). Like 8-OHDPAT, ipsapirone exhibits high affinity for 5-HT_{1A} receptor subtype and negligible affinity for the 5-HT_{1B}, 5-HT_{2C}, 5-HT_{2A}, and 5-HT_3 receptor subtypes (28). In rats, both presynaptic 5-HT_{1A} receptors (13) and postsynaptic 5-HT_{1A} receptors (18) have been reported to mediate 8-OHDPAT-induced hypothermia. In humans, ipsapirone-induced hypothermia has been suggested to be mediated by presynaptic 5-HT_{1A} receptors (22). In the present study, FH rats were found to be functionally subsensitive to the hypothermic effect of ipsapirone relative to Wistar rats. In this respect, our results are consistent with a previous report in which FH rats were found to be less sensitive to the hypothermic effect of 8-OHDPAT relative to SD rats (14). In a recent report, we have demonstrated B_{max} values for 5-HT_{1A} receptors labeled by [^{3}H]-8-OHDPAT to be significantly lower in the striatum and brainstem of FH rats compared to SD and Wistar rats (16).

The present study also demonstrates that m-CPP-induced increases in GH levels were significantly less in FH rats relative to Wistar rats. In monkeys, metergoline pretreatment completely blocks m-CPP-induced increases in GH levels (1). In rats, metergoline pretreatment also completely blocks clonidine-induced increases in GH levels (4,9). In a recent report from this laboratory we have demonstrated that clonidine stimulates GH secretion by activation of α_2-adrenergic heteroreceptors present on 5-HT nerve terminals which, in turn, enhance 5-HT activity via stimulation of postsynaptic 5-HT_{2C} receptors to promote GH releasing factor (4). Interestingly, in the same study, clonidine administration failed to increase GH levels in the FH rat strain (4). As mentioned earlier in the discussion, other 5-HT_{2C} receptor-mediated responses such as m-CPP-induced increases in plasma prolactin (6), decreases in food intake (36), and locomotor activity (5), have previously been reported to be attenuated in the FH rat strain relative to the Wistar and SD rat strains.

The present study further demonstrates that the baseline concentrations of 5-HT and its metabolite, 5-HIAA, did not significantly differ in the frontal cortex, hippocampus, hypothalamus, and striatum between the two rat strains. However, in brain stem, 5-HT and 5-HIAA concentrations were found to be significantly less in the FH rat strain relative to the Wistar rat strain. On the other hand, the 5-HT turnover rate was found to significantly higher in the hypothalamus and striatum in the FH rat strain relative to the Wistar rat strain. Because the hypothalamus is involved in the regulation of food intake, temperature, and neuroendocrine functions, it is tempting to speculate that increased 5-HT turnover in the hypothalamus in the FH rat strain may be responsible for the attenuated food intake, temperature, and neuroendocrine responses to 5-HT agonists. However, it is of note that we did not observe any significant difference in hypothalamic 5-HT_{2C} receptors labeled by [^{3}H]-mesulergine between FH rats and Wistar or SD rats (17). There are many examples in which serotonin receptor binding changes do not simply reflect concomitant serotonin functional sensitivity changes (23,31). On the other hand, decreased 5-HT and 5-HIAA levels in the brain stem may somehow be responsible for the decreased 5-HT_{1A} receptors labeled by [^{3}H]-8-OHDPAT (16) and functional subsensitivity of 5-HT_{1A} receptors mediating hypothermia observed in the present study.

Finally, it is necessary to ask whether the previously described increased plasma corticosteroids in FH rats (6) might be relevant to the present findings, and to the postulation of the FH rat strain as a genetic model for affective disorders. Depressed patients have been reported to have higher baseline levels of cortisol and also manifest functional subsensitivity to 5-HT agonist-induced increases in plasma prolactin levels (15,32), hypothermia (22), and also manifest blunted GH responses to clonidine (7,21), compared to normal controls. Brain serotonin changes have been implicated in the etiology of affective illness and mode of action of antidepressant and antimanic drugs (25). Thus, the FH rat strain may prove to be a useful genetic model for some neuropsychiatric disorders with possible abnormalities in serotonergic function such as depression, obsessive-compulsive disorder, and the eating disorders (8).

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