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RESEARCH ARTICLE

Serotonin Function Is Associated With Behavioral Response to a Novel Conspecific in Marmosets

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The function of the central nervous system neurotransmitter serotonin (5-HT) contributes to individual differences in impulsive behavior in humans and nonhuman primates. We investigated the relationship between 5-HT function and behavioral responses to a novel social scenario in marmosets. In the first study, marmosets (n = 10) were treated orally with fluoxetine HCl (FLX) or vehicle for two trial periods and exposed to a novel conspecific for a 20-min trial following each treatment. Levels of behavioral inhibition in response to a novel conspecific were quantified. The animals exhibited less inhibition toward the novel conspecific following the 14-day FLX treatment than they did following the vehicle treatment. In the second study we first characterized the parameters of the marmoset peripheral 5-HT system and further assessed the relationship between natural variation in peripheral 5-HT and 5-HIAA levels with behavioral inhibition in response to a novel conspecific (n = 14). Individual peripheral 5-HT and 5-HIAA levels were higher in animals that exhibited more inhibition in response toward the stranger. We conclude that serotonergic influences play a role in behavioral response to a novel conspecific in marmosets. Am. J. Primatol. 68:812–824, 2006.

Key words: serotonin; marmoset; social inhibition

INTRODUCTION

The monoamine neurotransmitter serotonin (5-HT) has been investigated as an important neural underpinning of personality [Cloninger, 1986] and temperament [Constantino & Murphy, 1996]. 5-HT measures and associated behaviors are relatively stable within individuals, which is consistent with the hypothesis that physiological substrates of characteristic behavior should be consistent within individuals. For example, cerebrospinal fluid (CSF) 5-HT levels

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[Anderson et al., 2002], as well as levels of CSF 5-hydroxy-3-indoleacetic acid (5-HIAA), a 5-HT metabolite, are stable within individuals over time (humans [Asberg et al., 1976] and macaques [Higley & Linnoila, 1997; Anderson et al., 2002]) and appear to be heritable [Higley & Linnoila, 1997]. Moreover, there is clear evidence that variation in 5-HT function is associated with specific behavioral repertoires. For instance, central 5-HT levels are inversely correlated with repeated suicide attempts in humans [Asberg et al., 1976], human and primate impulsive aggression [Higley et al., 1996; Roy et al., 1986], and primate social impulsivity [Fairbanks et al., 2001].

Markers of peripheral 5-HT may also appear to be highly consistent (i.e., trait-like and with genetic underpinnings) and associated with impulsivity. Platelet 5-HT, like central 5-HT, appears to be relatively stable within individuals over time [Anderson et al., 2004a]. Platelet 5-HT is highly correlated between mothers and newborns [Anderson et al., 2004b], and more strongly between monozygotic twins than dizygotic twins [Meltzer & Arora, 1988], which suggests that peripheral 5-HT function, like central 5-HT regulation, may be heritable. Peripheral measures are also associated with trait-like behavior. ''Melancholic'' patients show lower whole-blood 5-HT levels than controls [Perez et al., 1998]. Platelet binding affinity for paroxetine is lower in children who exhibit cognitive impulsivity than in others [Oades et al., 2002]. Boys rated as highly aggressive by their parents exhibit lower rates of 5-HT uptake to platelets [Stadler et al., 2004], and males with high life history aggression scores exhibit lower platelet 5-HT [Goveas et al., 2004]. The association between peripheral measures of serotonin function and behavior is likely a product of the correlation between central measures of central and peripheral 5-HT function (humans [Strawn et al., 2002] and macaques [Yan et al., 1993]), rather than peripheral action of 5-HT on behavior.

Impulsivity is thought to be the principal behavioral correlate of low 5-HT and 5-HIAA levels. Individuals with low 5-HT function have been shown to engage in higher rates of aggression (humans [Roy et al., 1986] and primates [Kyes et al., 1995]. Rhesus macaques with low 5-HT function display earlier dispersal from their natal group than those with higher 5-HT function [Mehlman et al., 1995]. These behaviors have been hypothesized to be attributable to a lack of behavioral inhibition [Fairbanks, 2001; Mehlman et al., 1994]. Targeted pharmacological manipulations have also borne out the relationship between the 5-HT system and behavioral inhibition. Men with a past history of conduct disorder report reduced impulsive behavior following acute treatment with 5-HT agonist fenfluramine [Cherek & Lane, 2000]. Selective serotonin reuptake inhibitor (SSRI) fluoxetine HCl (FLX) treatment, along with the SSRIs citalopram and paroxetine, has been shown to reduce impulsivity in pigeons [Wolff & Leander, 2002], and vervets treated with FLX exhibited a less impulsive response to intruder challenge [Fairbanks et al., 2001] than controls. It remains unclear whether general impulsivity or lack of inhibition in a social domain is most tightly linked with serotonin function in primates (including humans).

Behavioral inhibition may manifest itself in diverse ways within and between individuals. Various measures have been used to measure behavioral inhibition in human and animal models, such as novelty seeking and harm avoidance in humans, and dispersal, number of wounds, violent aggression, and risky locomotion in nonhuman primates [Cloninger, 1986; Higley et al., 1996; Mehlman et al., 1994]. The nature of an individual's response to an unfamiliar conspecific (i.e., intruder challenge) has been used as a measure of primate ''social'' impulsivity [Fairbanks et al., 2001]. Social impulsivity has been thought to be a

discrete domain of impulsive behavior [Fairbanks et al., 2001]. An individual's response to a novel conspecific (e.g., latency to approach, time spent in proximity to, bouts of attempting aggression toward intruder) illustrates the individual's propensity for risk-taking vs. restraint within a social context. Inhibited vs. impulsive behavior toward a novel conspecific may be considered to be opposite ends of a spectrum of social impulsivity, which includes not only the presence or absence of engagement of a novel conspecific but the quality of engagement (which may include the motivation to approach or aggress, or to be social or vigilant). In marmosets, threatening aggressive postures, such as anogenital threatening, flattening ear flaps, vocalizing, and attacking the intruder's cage, have been used to represent initiation of confrontation toward a novel conspecific [Cilia & Piper, 1997; Schaffner & French, 1997]. In the present study we assessed the characteristics of approach and engagement of a novel conspecific, which have been proposed to reflect individual differences in the spectrum of social inhibition/impulsivity [Fairbanks, 2001].

We investigated the involvement of the serotonergic system with social inhibition in a highly social, monogamous primate: the black tufted-ear marmoset (*Callithrix kuhlii*). To accomplish this goal we pharmacologically manipulated the system, characterized previously undocumented parameters of peripheral monoamine function in marmosets, and measured markers of peripheral 5-HT function. In the first study we conducted a repeated-measures, crossover-designed experiment in which animals were exposed to a novel conspecific both under control conditions and following FLX treatment ($n = 10$). We predicted that if the 5-HT system regulates social inhibition in marmosets, FLX treatment would alter social inhibition in the presence of a novel conspecific. In the second study we investigated whether natural variation in 5-HT function predicts variation in social inhibition in the intruder challenge paradigm. To accomplish this goal we validated an enzyme immunoassay to measure peripheral 5-HT and 5-HIAA in marmosets. Peripheral 5-HT and 5-HIAA levels were quantified, and parameters of peripheral 5-HT function in marmosets were evaluated. Finally, the relationship between natural variation in peripheral 5-HT measures and behavior in response to a novel conspecific was assessed.

MATERIALS AND METHODS: STUDY 1

Subjects

Ten marmosets (seven males and three females) were included in this study. These animals were maintained in five previously established pairings (three male–female pairs and two male–male pairs). The subjects' ages ranged from 2 to 10 years. The animals were housed in large indoor enclosures ($2.4 \times 1.6 \times 0.9$ m), fed once per day between 0600 and 1000 hr, and had access to water ad libitum. Their diets were consistent in content for the duration of the study. While olfactory and acoustic access to other marmosets was available, visual access was restricted with the use of large pieces of opaque plastic suspended between the cages. The animals were housed under a 12:12 hr light:dark cycle, and exposed to artificial ultraviolet light once during each trial period.

Procedure

Design

With the use of a within-subjects, crossover design, the subjects were administered oral FLX treatment and vehicle treatment (15 days for each

treatment). Four animals received FLX first, and six animals received vehicle first. Eight weeks elapsed between the experimental and control trials to prevent carryover effects of FLX treatment. Previous studies have shown that FLX has a halflife of 2–4 days, and its putative active metabolite, norfluoxetine, has a halflife of 7–15 days [Altamura et al., 1994; Preskorn, 1994]. Eight weeks was determined to be a conservative interval between trials. Basal blood draws were taken and drawn again at 1- and/or 2-week intervals during the treatment and control trials. Behavioral response to exposure to a novel conspecific occurred the afternoon following the last oral dosage of the trial.

Drug treatment

During the experimental phase the marmosets were treated daily with FLX (Eli Lilly, Indianapolis, IN) or vehicle over two 14-day trial periods. FLX was ingested orally, in juice, at an approximate dose of 3 mg/kg. Oral ingestion is effective in altering extracellular levels of 5-HT [Smith et al., 2000]. Pairs were allowed ad libitum access to juice that contained enough FLX for both animals. Juice alone was provided for animals as vehicle treatment during the control trial. The duration of drinking of the treated juice was noted during daily 10-min observations to ascertain that each animal likely ingested approximately half of the treated juice.

Additionally, blood was drawn three times during the 2-week course of FLX treatment (on trial days 1, 8, and 15) and twice during vehicle treatment (on trial days 1 and 15), between 0900 and 1300 hr. The time of physical restraint prior to sampling ranged from 1–5 min, and the time period from removal from the cage to sampling ranged from 10 to 90 min. The details regarding blood processing and assays are described below for study 2.

Novel conspecific trial

On trial day 15 the animals were removed from their home enclosures and placed in novel cages ($1.2 \times 0.8 \times 0.5$ m) overnight. The cages contained familiar items, such as branches and a nest tube. Following overnight social separation, animals were exposed to a same-sex unfamiliar conspecific for a 20-min trial on trial day 16. Lack of habituation to novel conspecific confrontation in marmosets was described previously [Cilia & Piper, 1997]; however, the crossover design of the present study controlled for potential carryover effects of repeated exposures to a stranger. During social separation from pair-mate and novel conspecific exposure the animals had auditory and olfactory, but not visual, access to the other experimental subjects. The animals had access to food, juice, and water ad libitum.

Exposure to a same-sex novel conspecific occurred between 0800 and 1200 hr. The novel conspecific was brought into the room in a transport cage ($0.4\,\text{m} \times 0.4\,\text{m} \times 0.4\,\text{m}$) covered with an opaque cloth to obstruct pretrial visual exposure. The transport cage was reinforced with metal wire mesh to prevent tactile access between the subject and conspecific. At the beginning of the trial the transport cage was attached to the temporary housing cage with a bungee cord. Visual obstruction of the test paradigm from other animals in the room was accomplished via partitions and cage positioning. The cloth was removed and the timer was started. The time between cage attachment and trial initiation was under 10 sec. For each 20-min trial the behavioral responses directed toward the unfamiliar conspecific were recorded, including latency to approach and leave, time spent in proximity, and bouts of directly facing (for definitions, see Table I).

TABLE I. Novel Conspecific Ethogram

Head orientation	Time spent engaged in head orientation away from or toward stimulus animal. The radius of an animal's possible head orientation was considered to be 360°. Head orientation toward novel conspecific included head orientation within 180° of the stimulus animal.
Latency to approach	Latency (seconds) to approach novel conspecific to within arm's reach of the animal for more than 1 second.
Latency to leave	Latency to withdraw from out of arm's reach of the novel conspecific for more than 1 second.
Proximity	The subject's cage was considered to be divided into four equally sized quadrants. Thus, subjects could maintain 5 degrees of proximity to novel conspecific: zero proximity (contact would be occurring if there were no barrier), in the closest quadrant, second closest, third closest, and furthest quadrant of the cage.
Direct face	Subject directs gaze directly at novel conspecific and does not desist for more than 1 second.

Furthermore, every 30 sec the absence or presence of locomotion, location in cage, and head orientation toward the novel conspecific were noted. Head orientation toward the novel conspecific that did not include a direct face or eye contact was scored as ''passive monitoring.'' Marmosets that showed the following patterns were considered to have lower social inhibition, based on previous studies of primate social impulsivity [Fairbanks, 2001]: more time spent in zero proximity, shorter latency to approach, less time spent in the area of the cage farthest away from the stimulus animal, less time spent passively monitoring novel conspecific presence, more bouts of directly facing, and longer duration of time before leaving the novel conspecific following the initial approach.

Statistics

A repeated-measures analysis of variance (ANOVA) was used to assess changes in behavior between FLX treatment and control conditions.

RESULTS: STUDY 1

Behavioral Response to Novel Conspecific

FLX treatment resulted in the differential expression of target behaviors compared to control conditions (see Fig. 1). Animals treated with FLX spent less time in the portion of the cage farthest from the intruder than under control conditions (F (1,9) = −10.88, $P < .05$). Passive monitoring (head orientation toward intruder without directly facing) of the novel conspecific was lower in FLX-treated animals than in controls (F (1,9) = 9.18, $P < .05$). FLX-treated animals directly faced the novel conspecific more frequently than controls (F (1,9) = 8.81, $P < .05$).

MATERIALS AND METHODS: STUDY 2

Subjects

Fourteen animals (nine adult males and five adult females, age range = 2–10 years) were used in this study. These animals were maintained in five previously established pairings (five male–female pairs and two male–male pairs).

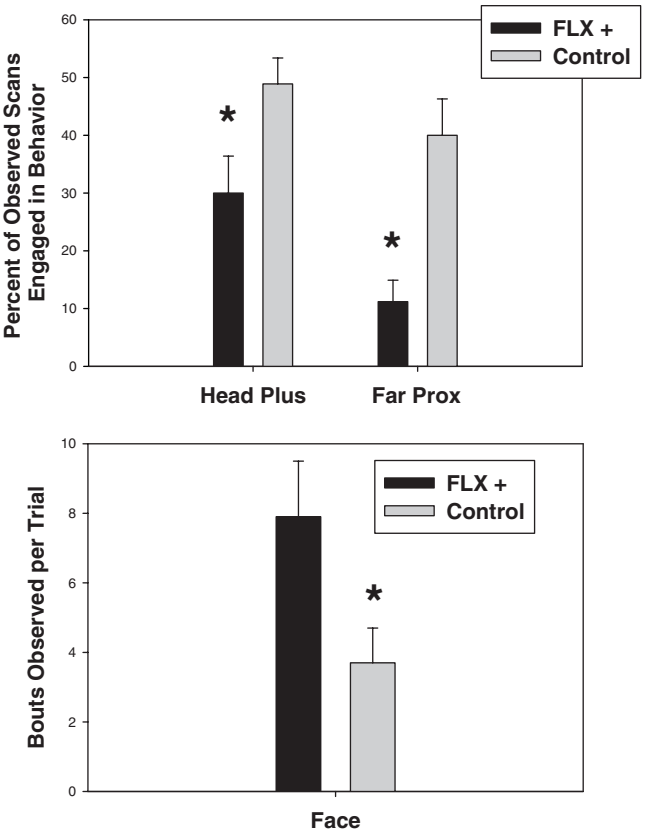

Fig. 1. Mean bouts (±SEM) passive monitoring of the novel conspecific's (HEADPLUS) tendency to stay far away from the novel conspecific (FARPROX), and bouts of directly facing the novel conspecific (FACE) under FLX or control conditions (n = 10; $^{*}P < .05$).

The marmosets were housed and maintained under conditions identical to those in study 1.

Procedure

Design

The animals were exposed to a 15-day trial that included vehicle treatment and blood draws, following which the animals were exposed to a novel conspecific under conditions identical to the first study. Blood was collected on day 1 and again on day 15, following social separation but prior to the novel conspecific trial, which occurred on day 16. Behavioral observations targeting social inhibition in response to a novel conspecific were conducted in a manner identical to that described for study 1.

Blood collection

Blood was drawn from the femoral vein of awake animals and decanted into EDTA-treated Vacutainers®. Blood was drawn on trial days 1 and 15 (prior to social separation and novel conspecific trial) during control conditions, between

0900 and 1300 hr. The time of physical restraint prior to sampling ranged from 1 to 5 min, and the period of time from removal from the cage to sampling ranged from 10 to 90 min. The preparation of blood included separation of plasma and platelets from whole blood. The blood was centrifuged for 10 min at $200 \times g$ at room temperature to obtain platelet-rich plasma (PRP). An aliquot of PRP was added to phosphate-buffered saline (PBS) and centrifuged at $1500 \times g$ for 20 min at 4°C. The platelet pellet was resuspended in distilled water. The platelets were counted from the PRP using an H-2000 Hematology Analyzer (Careside Inc., Culver City, CA).

5-HT and 5-HIAA assay validations

Assays were validated for the marmosets in two ways. First, whole blood from study 1 was assayed to assess the assay's sensitivity to peripheral response to drug treatment. This was considered to be a biological validation of the assay, as previous studies using high-performance liquid chromatography have shown that peripheral serotonin is reduced in response to FLX treatment [Anderson et al., 2004b; Blardi et al., 2002]. Second, parallelism to the standard curve was assessed. Human 5-HT and 5-HIAA enzyme immunoassays were purchased commercially (KMI Diagnostics, Minneapolis, MN) and the manufacturer's instructions were followed with a few alterations. Whole-blood and platelet samples were added to enzyme-linked immunosorbent assay (ELISA) plates that had been precoated with goat anti-rabbit IgG. 5-HT or 5-HIAA labeled with biotin, and 5-HT or 5-HIAA antiserum were then added immediately to the plate. The plates were sealed and incubated at 4°C overnight. Following washing, an antibiotin antibody was applied to the wells and incubated for 2 hr. Following conjugation, substrate was added for colormetric analysis. The plates were read at 405 nm with an ELISA plate reader, using Biolinx software (Biolinx Technology Co., Frankfurt, Germany).

Interassay variation was assessed with the use of both human serum pools and marmoset samples. Intra-assay coefficients of variance (CVs) ranged from 0.00% to 12.00%. Interassay CVs (pools and repeated samples) ranged from 0% to 42% in the 5-HT assays with a mean CV of 20%, and from 9% to 30% in the 5-HIAA assays with a mean CV of 21%. To control for variability between assays, individual samples from each condition were assayed on the same plate.

Statistics

Mean whole-blood 5-HT, platelet 5-HT, and platelet 5-HIAA (derived from the two samples collected from individuals at the beginning and end of the control trial period) were each determined to have unequal variances (Levene's test for equality of variances, $P < .05$), and were transformed for all analyses (log transformation for whole-blood and platelet 5-HT and inverse transformation for platelet 5-HIAA). Stability in the peripheral 5-HT and 5-HIAA measures was calculated using Pearson's correlation coefficients between sampling periods over the control trial. To further assess stability in 5-HT over time, CVs for each individual (except for one individual for which only one sample was available) were calculated by dividing the standard deviation (SD) by the mean of an individual's total sample concentrations and multiplying by 100. Independent-sample *t*-tests were conducted to assess the influence of sex, pair-mate sex, and age on behavior and 5-HT measures. Pearson's correlations were calculated between transformed serotonin measures and behavioral variables.

RESULTS: STUDY 2

5-HT and 5-HIAA Assay Validation

The samples collected in study 1 following FLX treatment showed reduced whole-blood and platelet measures of 5-HT and 5-HIAA. Whole-blood 5-HT, platelet 5-HT, and platelet 5-HIAA all decreased significantly following FLX treatment (F-tests, all $P < .05$), which suggests that the assay was biologically valid. Further, serial dilutions of marmoset whole-blood and platelet resuspensions paralleled the 5-HT standard curve, and platelet resuspensions paralleled the 5-HIAA standard curve. The lowest detectable values that could be differentiated from zero were 0.03 ng/ml for the 5-HT assay, and 0.15 ng/ml for the 5-HIAA assay. Cross-reactivity of 5-HIAA in the 5-HT assay was lower than 0.001%. Cross reactivity of 5-HT in the 5-HIAA assay was less than 0.01%.

Parameters of Marmoset Peripheral 5-HT Function

Stability of peripheral 5-HT over time

Individual whole-blood 5-HT was correlated between sampling days (i.e., days 1 and 15; $r = .77$, $P < .01$). Whole-blood 5-HT CVs of an individual between sampling points ranged from 5% to 63%, with a mean CV of 28%.

Relationship of age, sex, and social housing condition to normal 5-HT function

Age was not significantly correlated with any measure, including behavioral and serotonergic measures (Pearson correlations; all $P > .05$). Additionally, there were no significant sex differences in 5-HT measures (t-tests; all $P > .05$) or differences in subjects housed with a same-sex vs. opposite-sex partner (t-tests, all $P > .05$).

Peripheral serotonin measures and behavioral response to the novel conspecific

Peripheral measures of serotonin function were correlated with the expression of target behaviors (see Table II). Head orientation toward the novel conspecific was higher in animals with higher platelet 5-HIAA, which was reverse-scored due to transformation ($r = -.66$, $P < .05$). Animals that spent more time in zero proximity to the novel conspecific exhibited lower platelet 5-HT ($r = -.72$, $P < .05$). Latency to leave the novel conspecific was longer in animals with lower platelet 5-HT ($r = -.78$, $P < .01$), and the trend was the same for platelet 5-HIAA, which was reverse-scored due to transformation ($r = .53$, $P = .06$). Rates of directly facing the novel conspecific were higher in animals with lower whole-blood 5-HT ($r = -.57$, $P < .05$). Neither age nor sex was associated with these behaviors (both $P > .05$).

TABLE II. Pearson Correlations Between Behavioral and Biological Measures[†]

	WB 5-HT	PLA 5-HT	PLA 5-HIAA
Passive monitor	–0.48	0.32	–0.66**
Zero proximity	–0.028	–0.72**	0.22
Latency to leave	0.15	–0.79**	0.53
Direct face	–0.57*	0.17	–0.36

[†]Mean biological measures were transformed for analysis. Platelet values are expressed as ug/10^6 platelets.
*$P < 0.01$.
**$P < 0.05$.
WB, whole blood; PLA, platelet.

DISCUSSION

In the present study we established a relationship between function of the serotonin system and social inhibition in marmosets, using both an experimental paradigm and assessment of naturally occurring variation in serotonin function. Serotonin measures showed a consistent relationship with inhibited behavior toward novel conspecific in these two experiments, in which pharmacologically altered neural serotonin function and naturally low peripheral 5-HT and 5-HIAA levels were associated with similar behavioral profiles. For example, FLX-treated animals and individuals with naturally low peripheral serotonin had one or more of the following responses to a novel conspecific: more time spent as close as possible to a stranger, less time spent as far as possible from a stranger, more instances of directly facing a stranger, less time spent oriented toward a stranger without making eye contact, and a longer latency to leave a stranger following the initial approach–all of which indicate lower levels of inhibition. Thus 5-HT function appears to be involved in social inhibition in response to a novel social scenario in marmosets.

To fully investigate the relationship between natural variation in markers of serotonin function and social inhibition, we first characterized the parameters of naturally occurring peripheral serotonin function in marmosets. This study is the first to successfully characterize peripheral 5-HT function in marmosets using a less invasive method than is typically used in primates, which is ideal for longitudinal in vivo experiments. We have described previously unknown parameters of the marmoset serotonin system. Untreated subjects' 5-HT levels ranged from 500 to 4500 ng/ml in whole blood, and from 2 to 3400 ng/ml in platelets. The range for 5-HIAA was 95–450 ng/ml in platelets. No significant differences were detected between basal values in any peripheral 5-HT or 5-HIAA measure between sexes, nor did any values vary by social housing condition or age. Future studies may wish to employ a longitudinal design to confirm this lack of age-related serotonin decline, which has been noted in other primate species. Finally, the relative stability of whole-blood 5-HT over the control period suggests that, as in other species, 5-HT levels may be consistent and therefore potentially trait-like in marmosets.

The results presented here indicate that peripheral 5-HT activity in marmosets mirrors brain 5-HT function, as has been shown in other species. Molecular studies have highlighted the homology of the peripheral and central 5-HT systems by suggesting that genes that control 5-HT function act in tandem in the central nervous system (CNS) and peripheral systems [Heinz et al., 1998; Kaiser et al., 2002; Stoltenberg et al., 2002]. FLX acts by blocking the binding of 5-HT to its uptake sites (neurons [reviewed by Wong et al., 1995] and platelets [Bourdeaux et al., 1998]). Thus, our finding of a peripheral decline in 5-HT and 5-HIAA levels with FLX treatment is in accordance with our hypothesis, as well as with data from previous studies (rats [Bourdeaux et al., 1998], vervets [Raleigh et al., 1991], and humans [Blardi et al., 2002]). The action of FLX on peripheral measures of 5-HT and 5-HIAA concentrations in the predicted direction in this study illustrates the utility of peripheral 5-HT and 5-HIAA measures for psychopharmacological research. Further, the association of naturally occurring high peripheral serotonin levels and inhibition in response to a novel conspecific is in line with research that showed the same relationship between central measures of serotonin function and impulsive behavior in other primate species [Fairbanks et al., 2001; Heinz et al., 1998; Higley & Linnoila, 1997].

We used pharmacological manipulation of the 5-HT system to establish the causal role of the serotonin system in behavioral response to a novel social scenario. The animals were less socially inhibited following FLX treatment than following vehicle treatment in the present study. The immediate action of FLX is to block reuptake of serotonin to presynaptic neurons, which reduces 5-HT turnover [Wong et al., 1995] but gives 5-HT a longer time frame in which to exert its effects postsynaptically. Our results differ from previous findings, which suggest that FLX treatment reduces impulsivity in other species (e.g., pigeons [Wolff & Leander, 2002] and vervets [Fairbanks et al., 2001]). Our results may reflect a distinction between the short- and long-term effects of FLX on the serotonin system. FLX's action to decrease impulsivity/aggression was previously described following a course of treatment of 8 weeks or more [Fairbanks et al., 2001], whereas the present study included a treatment trial of 14 days. In addition to its known reuptake inhibition properties in the brain, long-term ($\geq$3 weeks) FLX administration has other effects that have not yet been fully characterized. These effects include desensitization of 5-HT_{1A} receptors [Briley & Moret, 1993] and increased 5-HT transporter translation in the brain [Hebert et al., 2001], which alter the inclusive functioning of the CNS 5-HT system. Indeed, it has been shown that there is a latency of SSRI action on depression [Wong et al., 1995]. Short-term changes in the 5-HT system may actually be associated with increased impulsivity in humans. Although one study showed that FLX treatment reduced the rate of suicide in depressed patients overall [Leon et al., 1999], in other studies high doses of FLX in the first month of depression treatment increased the likelihood of patient suicide [Goldblatt & Schatzberg, 1991; Jick et al., 1995]. It is possible that while FLX has long-term behavioral inhibition properties, its immediate effects actually lead to decreased behavioral inhibition.

To our knowledge, this is the first study to examine the relationship between serotonin function and social inhibition in a monogamous nonhuman primate. It may be hypothesized that the effect of FLX in increasing socially impulsive behavior may reflect a species difference in serotonergic regulation and social inhibition associated with the species' mating and social systems. Indeed, monogamous species were previously shown to differ from polygynous species in terms of physiological responsivity to intruders [Mendoza & Mason, 1986]. Since the relationship between natural variation in 5-HT levels and social inhibition in marmosets appears to be analogous to that in other primate species, it is only the behavioral response to FLX challenge that distinguishes marmosets. It may be that the architecture of the marmoset serotonergic system is such that FLX alters global 5-HT function in a more immediate fashion compared to other species, which may result in reduced serotonergic functioning in the short term and an accompanying increase in impulsivity. If impulsivity critically depends on the function of the 5-HT system in primates, then natural selection may have sensitized the system to avoid behavioral correlates that were not conducive to social structure maintenance in marmosets. Such maladaptive behavioral variation may involve dispersal timing [Mehlman et al., 1995] and social dominance acquisition [Fairbanks et al., 2004]. Marmoset reproductive success has been hypothesized to depend on a cooperative breeding social system [French & Schaffner, 1999] that is characterized by late dispersal (sibling-assisting infant care) and breeding-pair dominance [reviewed by French, 1997]. Therefore, marmosets may necessarily have a lower baseline tendency for impulsivity than other species, and an associated sensitization of the 5-HT system.

The present study provides evidence that monoamine function is associated with social inhibition in marmosets. The causal pathway appears to originate with serotonin function, since naturally low and pharmacologically altered peripheral 5-HT and 5-HIAA led to decreased behavioral inhibition. Future studies may address the influence of these physiological and behavioral characteristics on individual success in marmosets.

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