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ORIGINAL INVESTIGATION

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Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder

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Abstract *Rationale:* The role of serotonin in human aggression and impulsivity was evaluated by administering paroxetine or placebo for 3 weeks and comparing the effects on laboratory measures of aggression and impulsivity among male subjects with a history of conduct disorder. *Methods:* Twelve male subjects with a history of criminal behavior participated in experimental sessions, which measured aggressive and impulsive responses. Six subjects were assigned to placebo treatment and six subjects to placebo and paroxetine treatment. Aggression was measured using the point subtraction aggression paradigm (PSAP), which provides subjects with an aggressive and monetary reinforced response options. Impulsive responses were measured using a paradigm that gives subjects choices between small rewards after short delays versus larger rewards after longer delays. *Results:* Chronic administration of paroxetine (20 mg/day) for 21 days produced significant decreases in impulsive responses. Decreases in aggressive responses were evident only at the end of paroxetine treatment. Decreases in impulsive and aggressive responses could not be attributed to a non-specific sedative action because monetary reinforced responses were not decreased as has been observed following CNS sedation. *Conclusions:* Inhibition of serotonin reuptake by paroxetine is the possible mechanism for reductions in aggressive and impulsive responses. These results support other data linking serotonin function and aggression and impulsivity.

Keywords Aggression · Impulsivity · Serotonin · Paroxetine

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Introduction

A large number of scientific articles support a relationship between serotonin (5-HT) and human impulsive and aggressive behavior (Linnoila et al. 1983; Virkkunen et al. 1989). Studies in non-human species have also linked reduced 5-HT levels to aggressive and impulsive behavior (e.g. Higley et al. 1996). Pharmacological manipulation of the 5-HT system through tryptophan depletion or supplementation resulted in changes in predicted directions in self-reported mood/hostility (Cleare and Bond 1995) and laboratory measures of aggression (Bjork et al. 1999). Assessments of 5-HT response through challenge agents have revealed blunted 5-HT response in children with conduct disorder (Stoff et al. 1992) and personality-disordered individuals reporting high levels of aggression and impulsivity (Moss et al. 1990).

A number of studies with non-human subjects have established a relationship between 5-HT and laboratory measures of impulsivity. Decreases in impulsive behavior have been reported following administration of 5-HT reuptake inhibitors, 5-HT agonists (Soubrie 1986), and 5-HT releasing agents (Poulos et al. 1996). Lesioning of 5-HT pathways produced decreased impulse control (Ho et al. 1998). Collectively, these investigations suggest that reduced 5-HT plays a role in impulsive and aggressive behavior.

Serotonin reuptake inhibitors (SSRIs) such as fluoxetine have been found to decrease aggression in several species of animals (see review by Fuller 1996). Some investigators have suggested that patients with impulse and /or aggression disorders may respond favorably to SSRIs (e.g. Boyer 1992). Many clinicians have reported a reduction in anger outbursts among depressed, affect labile and post-traumatic stress disorder patients treated with fluoxetine (Rosenbaum et al. 1993). Fluoxetine compared to placebo treatment reduced self-report measures of irritability and aggression among personality disordered participants (Coccaro and Kavoussi 1997).

Critical to understanding the biology of impulsive/aggressive behavior is accurate measurement of these be-

haviors. In the present study, we describe a laboratory-based procedure in which subjects were exposed to tests of both impulsive and aggressive responding in the same experimental day. The impulsivity component involved a well-documented delay of gratification task (Mazur 1987; Logue 1995) in which subjects chose between a small reward available after a short delay and a larger reward available only after a longer delay. This procedure has demonstrated sensitivity in detecting impulsiveness in populations with impulse control difficulties (Logue 1995), and in measuring drug effects on impulsive behavior (Cherek and Lane 2000). The aggressive responding component employed the point subtraction aggression paradigm (PSAP) (Cherek 1992). The external validity of this procedure has been established in studies demonstrating differences between violent and non-violent individuals (Cherek et al. 1997).

The present investigation assessed the effects of paroxetine (a 5-HT reuptake inhibitor) on aggressive and impulsive behavior of individuals with a history of antisocial behavior. We postulated that, in accord with previous human studies, increasing 5-HT activity in the CNS would produce decreases in aggressive and impulsive responding. An earlier study with *d,l*-fenfluramine, which releases 5-HT and dopamine, reported significant decreases in aggressive and impulsive responses among a group of CD male subjects (Cherek and Lane 1999). The present experiment would allow us to contrast the results of chronic 5-HT reuptake inhibition with our previous studies using 5-HT releasing agents.

Materials and methods

Subjects

Twelve male subjects on parole were recruited via newspaper advertisements into a laboratory study involving measures of behavior and paroxetine administration. Informed consent was obtained during intake interviews. All subjects had been convicted of at least one felony and were incarcerated for some period of time. The specific consent forms and all procedures were reviewed and approved by the IRB for the Health Science Center.

Seven subjects reported no current alcohol use, while the other subjects reported weekly beer drinking ranging from 4 to 12 beers per week. Eight of the subjects reported smoking five to ten cigarettes per day. None of the subjects reported current illicit drug use. Most of the subjects reported prior use of illicit drugs: marijuana (ten), cocaine (five), diazepam (three), amphetamines (three), opiates (two) and LSD (two). Subjects were required to provide drug free urine once per month as a condition of their parole.

Recruitment and screening

To assess cognitive functioning, all subjects were administered the Shipley Institute of Living Scale (Shipley Boyle 1967), a test of general intellectual aptitude that includes a 40-item vocabulary test and a 20-item abstraction test. Shipley scores gave estimates of the WAIS IQ score. The range on all WAIS estimate scores was within the normal range of one standard deviation.

Subjects reporting any medical or psychiatric illness were excluded. All subjects were screened for psychiatric illness using a mental status exam and the Structured Clinical Interview for DSM-IV (SCID-P), a standardized psychiatric interview (First et al. 1996). Subjects were excluded for any axis I disorder, except past substance abuse or dependence. The SCID-II Structured Clinical Interview was also used to determine if subjects met criteria for childhood conduct disorder by 15 years of age.

The final sample included 12 subjects with a history of conduct disorder. Six were assigned to placebo and six were assigned to paroxetine treatment.

Extraneous drug use

Collecting a urine sample and expired air sample each day the subjects came into the laboratory monitored recent alcohol and drug use. The alcohol content of the expired air was measured using an Alcosensor III (Intoximeter, Model 3000, St Louis, Mo., USA). The urine sample was subjected to a complete drug screen analysis utilizing the Enzyme Multiple Immunoassay Technique Drug Abuse Urine Assay (EMIT d.a.u. by Sylva Corporation, Palo Alto, Calif., USA). This procedure screened for all known drugs of abuse and several hundred therapeutic compounds. Detection of any drug in the subject's urine or alcohol in the air sample resulted in the removal of the subject from the study. Urinanalysis results were provided within 7 h.

Apparatus

During experimental sessions, subjects sat in a 1.2 m×1.8 m sound-attenuated chamber. Continuous masking noise was provided by a fan motor from an airconditioning unit mounted at the top of the rear wall and an overhead light provided illumination. The chamber contained a VGA monitor and a 10 cm×43 cm×25 cm response panel. Three Microswitch pushbuttons labeled "A", "B" and "C" were mounted on the top of the response panel in a straight line 10 cm apart. The cable coming into the back of the response panel was of sufficient length to allow subjects to place the response panel on their lap during sessions. The monitor and response panel were linked to a Pentium-based computer outside the chamber using an interface card (Med Associates, Inc., Georgia, Vt., USA) and a customized hardware/software system. This computer and interface controlled and recorded all experimental events.

Instructions for PSAP

Prior to participation, subjects were provided with information about potential earnings, urine drug testing, breath alcohol testing and psychiatric screening. Subjects were told that they could expect to earn from $4.00 to $8.00 per session and additional bonuses were provided for drug-free urines and study completion.

Prior to the first session, subjects were shown a diagram of the computer monitor and response panel and read the following instructions:

"Today, you will be able to earn money by working at the response console. This is a drawing of the response panel and computer monitor. You will be participating with other persons in this study. These other people will have similar response panels and monitors. These other people are located at another facility.

As the drawing illustrates, the response panel contains three buttons labeled A, B and C. The C button will not be used in this study. When each session starts, the letters A and B, and a counter will appear on the computer screen. The counter will be at zero. Pushing the A button will cause the B letter to go off the screen. Pushing the A button approximately 100 times will cause the A letter to go off the screen, and add 15 cents to the counter. After about 1 s, the A and B letters will come back on the computer screen. At that time, you can continue to press button A or switch to button B.

During the session the counter on your computer screen may become larger and 15 cents will be subtracted. After the 15 cents is subtracted, the counter will return to its normal size. This means

that one of the other persons has subtracted 15 cents from your counter by pushing button B on his response panel. The money that this person subtracts from your counter is added to his counter.

If you push button B on your response panel, the A letter will go off the screen. After you have pushed button B approximately 10 times, the letter B will go off the screen and 15 cents will be subtracted from the other person's counter. After about 1 s, the A and B letters will come back on the computer screen. You can continue to press button B and subtract additional money from the other person or switch to button A. If you subtract money from the other person, it will not be added to your counter. Remember, money subtracted from your counter by the other person is added to that person's counter."

No additional information regarding the procedure was provided. Portions of the instructions were repeated if the subjects asked questions.

Point subtraction aggression paradigm (PSAP)

The two-option version of the PSAP software program was used to measure aggressive and non-aggressive responding.

Response options

During experimental sessions subjects were provided with two response options: (1) a monetary reinforced response, and (2) an aggressive response. Pressing button A was maintained by a fixed-ratio (FR) 100, i.e. 100 consecutive responses, schedule of monetary reinforcement. Completion of the FR100 on button A incremented the counter by 15 cents. Subjects were paid the amount shown on their counter at the end of the session. Ten consecutive presses on button B (FR10) ostensibly resulted in the subtraction of 15 cents from a fictitious person paired with the subject during the session. Responding on button B was defined as aggressive, since such responding ostensibly resulted in the presentation of an aversive stimulus, i.e. loss of money, to another person. Once a subject selected either button A or B, then only that response option was available until the required ratio of 10 or 100 responses was completed, and then both response options were available again.

Provocation

Subtracting money from the subjects occasioned aggressive responding. Monetary subtractions were presented randomly via a computer program, which selected intervals between 6 and 120 s for successive subtractions. These monetary subtractions were attributed to the fictitious other person paired with the subject.

Consequences of aggressive and escape responding

Aggressive responding was maintained by the initiation of provocation-free intervals during which no money was subtracted from the subjects. Besides ostensibly subtracting money from the other person (option B), completing an FR10 on button B also initiated a 125-s interval during which no additional subtractions occurred. After the 125-s interval elapsed monetary subtractions were again presented. At least one 15 cent subtraction had to occur before each 125-s provocation-free interval could be initiated. These contingencies ensured that subjects could not avoid monetary subtractions, but they could reduce the number of subtractions occurring in each session by responding on button B. Thus, subjects were periodically provoked throughout the session, and in the absence of aggressive responding, 20–25 subtractions were presented in a session.

Instructions for impulsivity (IMP) sessions

After receiving instructions for the PSAP sessions, subjects were shown a diagram of the computer monitor and response panel and read instructions relating to the IMP sessions. The following instructions were provided for IMP sessions.

During sessions, both the letters A and B will appear on the screen in yellow color. First, you must choose one of the letters by pressing either the A or B button. The letter you have selected will remain on the screen, and the other letter will disappear. Now, wait until the letter begins to flash, and press the button again. An amount of money will then be added to the counter, and both letters will again appear on the screen. During these sessions, you will only have to press the button twice to earn money.

No additional information regarding the procedure was provided. Portions of the instructions were repeated if the subjects asked questions. Subjects were not provided any information regarding the length or number of sessions to be conducted (see below).

Impulsivity (self-control) paradigm

A modified version of the self-control paradigm introduced by Mazur (1987) was used to measure impulsive behavior. Subjects were given opportunities to choose between a smaller more immediate reinforcer versus a larger more delayed reinforcer. Choice of the smaller more immediate reinforcer was defined as impulsive.

During IMP sessions subjects were provided with two response options: (1) an impulsive option (A) and (2) a self-control option (B). Both the A and B letters appeared on the screen at the beginning of each trial. The subject selected a letter by pressing the corresponding button on the response panel. The selected letter remained on the screen, and the other letter disappeared. After a delay, the letter began to flash off and on, and a single response on that button added a monetary value (either 5 or 15 cents) to the counter and the letter disappeared. The subsequent appearance of the two letters 2 s later signaled the beginning of the next trial. Button A responses were operationally defined as impulsive. The delay to reinforcement was 5 s and the reinforcer amount was 5 cents. Because the session duration was not a fixed time, but instead controlled by the number of trials, there was no monetary advantage to the subject for choosing the A option. The delay associated with the A option was fixed.

Button B responses were operationally defined as self-controlled. The delay was longer, but the reinforcer magnitude was greater than for the A response. At the beginning of each session, the delay associated with the B response was 15 s, and the reinforcer was 15 cents. Following each A response, the B delay was shortened by 2 s, to a minimum of 7 s. Conversely, following each B response, the B delay was lengthened by 2 s. In this way, a subject repeatedly choosing the B option would be exposed to increasingly longer delays for the 15 cent reinforcement to a maximum of 113 s.

Impulsivity was measured as the number of choices of the smaller, more immediate (A option) reinforcer. Because the number of impulsive choices could be the same for two subjects despite differences in the patterns of their choices, the average delay maintained for the B (self-control) option and the longest delay achieved were also measured.

Paroxetine

Like fluoxetine, paroxetine is a 5-HT reuptake inhibitor, which interacts with the 5-HT transporter site, and selectively inhibit the reuptake of 5-HT and is regarded as one of the more potent inhibitors of 5-HT reuptake (Nathan et al. 1995). Paroxetine is considered to be as effective as fluoxetine in the treatment of depression (Charney et al. 1995). Paroxetine was selected because it has a much shorter half-life (20 h) and produces no active metabolites (Tollefson 1995). These characteristics are better suited for a placebo-drug-placebo design, which requires fairly rapid elimination

of the drug for evaluation of placebo effects following drug administration.

A 20 mg/day dose of paroxetine was selected. This dose is a therapeutic dose and generally well tolerated (Wernicke et al. 1989). Placebo or paroxetine was administered orally in #00 opaque capsules at 8:30 a.m., 30 min before the first PSAP session on Tuesday and Thursday in the laboratory. After the first baseline week, subjects were given a Medication Event Monitoring System (MEMS, Aprex Corp.) prescription bottle containing enough capsules until the next scheduled laboratory visit. Subjects were instructed to take one capsule each morning between 8:30 and 9:00 a.m.

The consent form listed the following possible side effects: stomach upset, drowsiness, dry mouth, difficulty sleeping and subjects were told that some individuals might experience a delay in the time to ejaculation. Each day the subjects came into the laboratory they were given a list of a wide array of 23 possible side effects. They were asked to indicate if they had experienced any of those listed and to describe any other side effects not on the list.

Procedure

Subjects participated two (Tuesday, Thursday) days a week for 8 consecutive weeks. The urine and breath samples were obtained on arrival in the laboratory at 8:00 a.m. Subjects participated in four PSAP sessions conducted at 9:00, 10:30 a.m., 1:00 and 2:30 p.m. These sessions alternated with IMP sessions that began at 9:30, 11:00 a.m., 1:30 and 3:00 p.m. Subjects were given a 5-min break outside the testing chamber between each PSAP and IMP session. Between sessions subjects waited in a common area containing a television and magazines. Lunch was provided at 12:00 p.m. PSAP sessions were 25 min, and IMP sessions were of variable duration and ended after 50 trials. The length of IMP sessions depended upon the subject's choices. If subjects selected all self-control (B) choices the session would be 53 min, and if they selected only impulsive choices (A) the session would be about 8 min. Since the number of trials was fixed, selecting the self-control option on every trial maximized earnings. Subjects did not receive any information regarding session duration or the number of sessions. Actual IMP sessions were between 15 and 25 min because all subjects chose both options.

For both the placebo and paroxetine groups, week 1 was baseline (no capsules) and during weeks 2 and 3 all subjects received placebo. The paroxetine subjects received 20 mg/day for weeks 4, 5 and 6, while placebo subjects continued to receive placebo capsules. The paroxetine subjects were returned to placebo capsules during weeks 7 and 8, the placebo subjects continued with placebo capsules.

Compliance with treatment regimen

During each visit to the laboratory, computer software read the cap of the subject's MEMS bottle. Displayed on the computer screen were the dates and times of all bottle openings. On Friday mornings (excluding the baseline week), subjects came into the laboratory to have a blood draw for paroxetine plasma level determinations. This was conducted in the Department clinic and samples were sent to the manufacturer for analysis. Subjects were previously instructed that failure to detect paroxetine in their plasma could be grounds for dismissal from the study.

Evaluation of instructional deception for PSAP sessions

Subjects were given a questionnaire at the end of the day which asked them to: (1) estimate the number of subjects they had been paired with that day, (2) describe these other subjects, and (3) estimate whether they had subtracted more or less money than the other subjects. This questionnaire is used routinely to assess whether or not the instructional deception regarding the other persons had been established and maintained throughout the experiment.

Assessment of understanding of instructions and response strategies for impulsivity paradigm

Following the last session, subjects were given a questionnaire to determine their understanding of the response options and their strategy. The questions were: (1) did you notice a difference between the A and B response option? If yes, what was it?; (2) were you trying to earn as much money as possible?; (3) which do you think was the best way to earn money? Choose only the A option, choose only the B option, choose both A and B options equally, or choose both A and B option, but not equally. Why is this the best method? and (4) did you use the best way to make money? If no, why not?

Questionnaires

The following questionnaires were completed at the end of the study. Subjects completed three questionnaires related to aggression: (1) Buss-Perry Aggression Questionnaire (Buss and Perry. 1992), (2) Retrospective Overt Aggression Scale (ROAS) (Sorgi et al. 1991), and (3) the State-Trait Anger Expression Inventory (STAXI) (Spielberger et al. 1985). In addition, subjects completed the Barratt Impulsivity Scale-BIS 11 (Barratt 1985), a questionnaire frequently used to assess impulsivity.

Statistical analysis

The following data were analyzed for both groups: aggressive responses per minute, monetary reinforced responses per second, the number of impulsive responses, the longest delay (s) achieved for the larger reward and the average delay maintained for the larger reward. Each of the four conditions was analyzed separately, week 1 of baseline, weeks 2 and 3 of placebo, weeks 4,5 and 6 of either paroxetine 20 mg/day or placebo, and weeks 7 and 8 of placebo administration to both groups. An ANOVA analysis was performed with one between-subjects factor, group (placebo versus paroxetine), and two within-subject factors, day with two to six levels across different conditions and session (four per day). Post hoc analysis was conducted using the Tukey HSD Test (Winer 1971). One subject in the placebo group was excluded from the analysis of impulsive responses, because he failed to emit any impulsive responses during the initial placebo condition. An additional analysis was performed on the aggressive response data to determine if there was a simple main effect of days for subjects in the placebo and paroxetine groups. A *t*-test comparing the last day of paroxetine treatment with placebo treatment was also performed.

Results

Demographics

The paroxetine and placebo groups did not differ regarding estimated IQ (95.83 versus 97.66), age (33.5 versus 31.8 years), education (11.8 versus 11.5 years) or number of drugs used previously (5.1 versus 4.8).

Instructions

All subjects reported that they had been paired with other subjects during the PSAP sessions. With respect to the Impulsivity/Self Control Paradigm, reports from the subjects indicated that they understood that the way to maximize earnings was to select the larger reward. Subjects

most often reported that they did not maximize their earnings because they could not tolerate the long delays associated with B option, and thus earned less money than possible.

Compliance

All 12 subjects had better than expected compliance as recorded by MEMS bottles.

Approximately 80% of the openings occurred between 8 and 9 a.m. each morning and all subjects had one opening per day. Plasma levels of paroxetine were detected in the six subjects receiving 20 mg/day paroxetine. The initial levels after the first week of paroxetine varied from 0–23 ng/ml, and tended to increase over the next 2 weeks of paroxetine treatment, reaching levels as high as 51 ng/ml. Both plasma levels and MEMS bottles indicated a high level of compliance among the subjects.

One paroxetine subject reported delayed ejaculation, while the other subjects reported no side effects during paroxetine or placebo treatment. Although symptoms have been associated with SSRI discontinuation (Hindmarch et al. 2000), none of subjects reported any side effects during the return to placebo treatment following 3 weeks of paroxetine.

Questionnaire data

Subjects in the paroxetine and placebo group did not differ on any of the questionnaire scores or subscales of the Buss-Perry Aggression Questionnaire, ROAS, STAXI and BIS-11.

The total Buss-Perry Aggression Scores were comparable for the paroxetine and placebo subjects (68.3±11.0 versus 65.2±7.5). Total ROAS scores were 7.3±1.7 versus 7.0±1.2, and total BIS-11 scores were 63.2±5.7 versus 68.2±3.8. STAXI scores were also similar: (a) Ax/Out scores were 14.5±1.7 versus 15.2±0.9 (Anger-Out an eight-item scale measuring how often anger is expressed toward other people or objects in the environment); (b) S-Anger scores were 11.2±1.0 versus 10.5±0.3 (State Anger ten-item scale measuring the intensity of angry feelings); and (c) T-Anger scores were 17.2±3.2 versus 18.5±1.9 (Trait Anger a ten-item scale measuring disposition to experience anger).

Analysis across all four sessions

Data in this section includes all four PSAP or all four IMP sessions conducted each experimental day during four different conditions: week 1 of baseline, weeks 2 and 3 of placebo, weeks 4, 5 and 6 of paroxetine or placebo, and weeks 7 and 8 a return to placebo administration.

Monetary reinforced responses per second

Monetary reinforced responding remained essentially unchanged across all conditions in both groups of subjects. The following statistical analyses (ANOVA) were performed on the number of monetary reinforced responses per second during each session. Under baseline conditions the placebo and paroxetine subjects had similar rates of responding (4.94 versus 4.96 responses/s), the main effect of group was not significant (F=0.00, df=1,10, P=0.96), and effects of day, session and all interactions were not significant. During the first 4 days of placebo conditions the placebo subjects averaged 5.33–5.53 responses/s and the paroxetine subjects averaged 4.96–5.24 responses/s. The main effect of group was not significant (F=1.31, df=1,10, P=0.28), nor were the effects of day, session and all interactions. In addition, the main effect of group was not significant during the 6 days of paroxetine or placebo treatment (F=0.93, df=1,10, P=0.36) or during the last 4 days of placebo treatment (F=2.38, df=1,10, P=0.15). The placebo subject's monetary response rate was 5.62–6.05 responses/s during placebo treatment and 5.74–6.06 during post-treatment placebo sessions. Response rates for paroxetine subjects were 5.34–5.60 and 5.25–5.41 responses/s. No other main effects or interactions were significant for the number of monetary reinforced responses per second.

Aggressive responses/min

Figure 1 shows the number of aggressive responses per minute under all four conditions expressed as a percent of the mean placebo value over the 4 initial placebo days (weeks 2 and 3) for the six subjects in the placebo group (clear squares) and six subjects in the paroxetine (black squares) group. Baseline rates of aggressive responses per minute were comparable for the paroxetine (12.90±3.52) and placebo groups (12.98±2.52). Both groups of subjects decreased aggressive responding over the baseline condition (days 1 and 2). Under baseline conditions, the main effect of group was not significant (F=0.00, df=1,10, P=0.98), and effects of day, session and all interactions were not significant. On days 3–6 of placebo treatment the aggressive responding was very similar. During the first 4 days of placebo conditions, the main effect of group was not significant (F=1.99, df=1,10, P=0.19) nor were the effects of day, session and all interactions. During days 7–12, the placebo subjects' aggressive responding remained relatively stable. The paroxetine subjects' aggressive responding steadily declined, but appeared considerably lower than placebo group only on the last day of paroxetine treatment (day 12). During the return to placebo treatment (days 13–16), the aggressive responding of the paroxetine subjects remained suppressed relative to the placebo group. The main effect of group was not significant during the 6 days of paroxetine or placebo treatment (F=2.18, df=1,10, P=0.17) or during the last 4 days of placebo

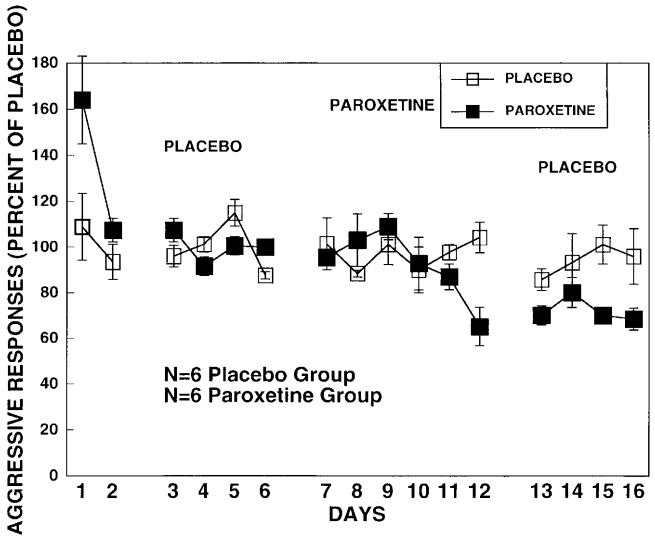

Fig. 1 Number of aggressive responses per minute under all four conditions expressed as a percent of the mean placebo value over the 4 initial placebo days for the six subjects in the placebo group (*clear squares*) and six subjects in the paroxetine (*black squares*) group. The *vertical lines* at each data point represent ±1 SEM

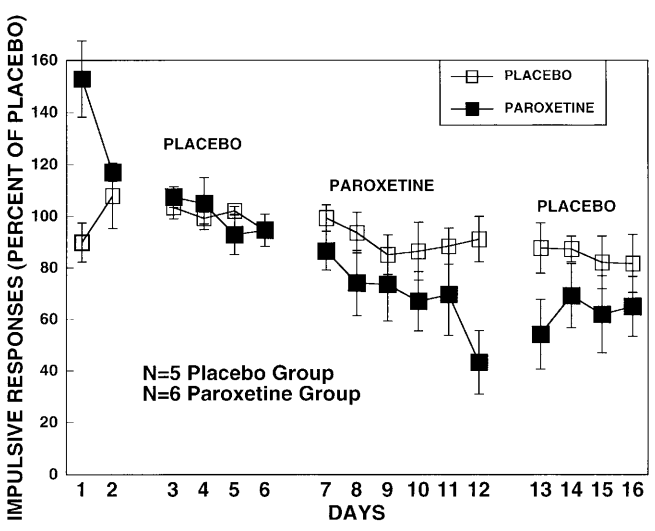

Fig. 2 Number of impulsive responses under all four conditions expressed as a percent of the mean placebo value over the 4 initial placebo days for the five subjects in the placebo group (*clear squares*) and six subjects in the paroxetine (*black squares*) group. The *vertical* lines at each data point represent ±1 SEM

treatment (F=3.24, df=1,10, P=0.10). No other main effects or interactions were significant for the number of aggressive responses per minute.

An additional post-hoc ANOVA analysis on aggressive responses was conducted to determine if there was a simple main effect of days within each group across the placebo, paroxetine or placebo treatment and post-treatment placebo sessions. The main effect of days was significant for the paroxetine group (F=3.34, df=10,50, P=0.02) but not for the placebo group (F=1.44, df=10,50, P=0.24). A paired t-test comparing the mean of the initial placebo sessions and the last day of paroxetine or placebo treatment indicated a significant decrease for the paroxetine group (t=2.77, P=0.03) but no difference for the placebo group (t=0.74, P=0.42).

Number of impulsive responses

Figure 2 shows the number of impulsive responses under all four conditions expressed as a percent of the mean placebo value over the 4 initial placebo days (weeks 2 and 3) for the five subjects in the placebo group (clear squares) and six subjects in the paroxetine (black squares) group. Under baseline conditions, the placebo subjects had a slightly larger number of impulsive responses per session (32.3±3.63 versus 25.40±4.08; t=1.40, P=0.20). The main effect of group was not significant (F=2.29, df=1,9, P=0.16), and effects of day, session and all interactions were not significant. On day 2 of baseline and days 3–6 of placebo treatment the number of impulsive responses in both groups was very similar. During the first 4 days of placebo conditions, the main effect of group was not significant (F=1.28, df=1,9, P=0.28), nor were the effects of day, session and all interactions. During days 7–12, the placebo subjects had a slight decrease in the number of impulsive responses. The paroxetine subjects showed an even greater decline, with the lowest number of impulsive responses occurring on the last day of paroxetine treatment (day 12). In contrast, the main effect of group was significant during the 6 days of paroxetine or placebo treatment (F=10.34, df=1,9, P=0.01) and during the last 4 days of placebo treatment (F=13.31, df=1,9, P=0.005). The main effect of session was also significant in these two conditions (F=3.36, df=1,9, P=0.03 and F=3.24, df=1,9, P=0.04). This effect was due to a slight reduction in the number of self-control responses in the fourth (last) session of the day, which occurred presumably because impulsive choices shortened the duration of this last session. This effect was observed in both groups. No other main effects or interactions were significant for the number of impulsive responses. During the return to placebo treatment (days 13–16), the impulsive responses of the paroxetine subjects remained suppressed relative to the placebo group.

Post hoc analysis of the 6 days (weeks 4–6) of paroxetine or placebo treatment indicated that the two groups were significantly different on days 7, 8 and 11 (P<0.05) and on day 12 (P<0.01). Post hoc testing of the 4 days (weeks 7 and 8) of placebo following paroxetine or placebo treatment indicated that the two groups differed on days 13 and 14 (P<0.01) and on days 15 and 16 (P<0.05).

Additional measures were analyzed relating to the IMP sessions: (1) the longest delay achieved for the self-control response option, and (2) the average delay that subject's maintained for the self-control (B) option. The paroxetine group achieved a significantly longer delay

on the self-control option, compared to placebo group during the 6 days of paroxetine treatment (F=7.61, df=1,9, P<0.02) and during the next 4 placebo days (F=8.60, df=1,9, P<0.01). The average delay maintained on the self-control option was greater for the paroxetine group only during the period of paroxetine treatment days 7–12 (F=5.31, df=1,9, P<0.04).

Analyses of the reaction times (time between letter beginning to flash and the appropriate button press response) for responding to the impulsive option (A) and the non-impulsive option (B) during the 6 days of paroxetine or placebo treatment were performed to determine if administration of paroxetine altered the subjects' reaction time. The reaction times to the impulsive option A did not differ between placebo and paroxetine subjects (F=0.26, df=1,9, P<0.62). Analysis of the reaction times for option B (self-control) indicated no difference between the two groups (F=0.18, df=1,9, P<0.67).

Discussion

Monetary reinforced responses were unaffected by chronic 21-day treatment with 20 mg/day paroxetine. No differences in the rate of monetary reinforced responding were observed between placebo and paroxetine groups across baseline, placebo, paroxetine and a return to the placebo conditions. This lack of effect is in contrast to the increased monetary reinforced responding observed following administration of a 5HT-releasing agent *d,l*-fenfluramine (Cherek and Lane 1999). The monetary response option within the PSAP procedure provides an estimate of specificity of drug action by comparing effects on monetary and aggressive responding (e.g., Cherek and Steinberg 1987). For example, non-specific sedative effects would be indicated by proportional decreases in both response measures. Because the chronic administration of paroxetine did not decrease the rate of monetary reinforced responding, the observed decreases in both aggressive and impulsive responses cannot be attributed to a non-specific sedative action of paroxetine.

Previous research has reported that 4 weeks of paroxetine treatment produced decreased self-reported negative affect and hostility in normal controls (Knutson et al. 1998). Chronic treatment with a serotonin reuptake inhibitor, fluoxetine, reduced scores on a modified version of the Overt Aggression Scale among personality disordered males (Coccaro and Kavoussi 1997). In the present study, 3 weeks of paroxetine treatment decreased a laboratory measure of aggressive responding compared with placebo subjects, but the group×treatment interaction was not significant. Additional analysis did indicate a significant change in aggressive responding over the course of the study among paroxetine treated subjects that was not observed in placebo subjects. Aggressive responses on the last day of paroxetine treatment were significantly lower than responses during initial placebo treatment. The same within-group comparison among placebo subjects indicated no change in aggressive responses.

Several factors could account for this significant effect, while the group×treatment interaction was not significant. First, the number of subjects in each group is small (n=6). The research design is complex, involving four different experimental conditions. Most importantly, the ANOVA analysis for the group×treatment interaction takes into account changes across all 6 experimental days of paroxetine or placebo treatment. If paroxetine effects on aggressive responding were delayed, i.e. after 2 or more weeks, then changes might not be detected in an analysis across all these days. In the present study, paroxetine treatment was initiated for 21 days. Perhaps this amount of time was insufficient to produce a significant reduction in aggressive responding. Coccaro and Kavoussi (1997) noted that clear differences in self-report measures of irritability and aggression between fluoxetine and placebo treated subjects did not emerge until after a month of treatment. However, most of the reductions observed in their study involved verbal aggression or aggression directed at objects. Aggression directed at other people was not affected. Three weeks of paroxetine treatment, however, is sufficient to produce a favorable clinical response in depressed patients (Charney et al. 1995).

The additional analysis performed within groups showing significant changes over days and during the last day of paroxetine treatment support a pharmacological effect on aggressive responses. A previous laboratory study of ten CD+ subjects found that *d,l*-fenfluramine significantly decreased aggressive responding (Cherek and Lane 1999). In addition, a more recent study found that the acute administration of *d*-fenfluramine also significantly decreased aggressive responding (Cherek and Lane 2001). The present study also found a decrease in aggressive responding associated with chronic reuptake inhibition of 5-HT rather than acute release of 5-HT.

There was no difference between the percent of trials on which the impulsive option was selected in the placebo and paroxetine groups (t=0.83, P<0.44). In the present study, the 12 CD+ subjects selected the impulsive option on 58.5% of the trials, which is very similar to 55.4% of trials in which ten CD+ subjects selected the impulsive option in a recent *d,l*-fenfluramine study (Cherek and Lane 1999). Such a preference for the impulsive option is similar to our data from previous studies using this procedure. These studies reported much higher preferences for the impulsive option than has been observed in studies conducted with college students (<5%) that have reported marked preferences for the self-control option (e.g. Logue 1995).

Impulsivity may have a biological basis, which most frequently has been related to serotonin function (Depue and Spoont 1986; Soubrie 1986). Reductions in impulsivity have also been self-reported by borderline personality patients receiving fluoxetine treatment (Cornelius et al. 1991). The significant reduction following paroxetine treatment in the present study and the significant reduction in impulsivity by *d,l*-fenfluramine (Cherek and Lane 1999) supports a relationship between impulsive behav-

ior and serotonin. Non-human studies employing a very similar impulsivity procedure have shown that acute doses of *d*-fenfluramine reduced impulsive responses in rats (Poulos et al. 1996). Other studies employing delay to reward procedures also reported decreased impulsive responses following administration of serotonin reuptake inhibitors, serotonin agonists (Soubrie 1986), or increased impulsiveness following serotonergic lesions (Ho et al. 1998). The present data are therefore consistent with these previous studies, suggesting that serotonin is involved in the regulation of impulsivity.

Both aggressive and impulsive responses of paroxetine subjects remained suppressed relative to placebo subjects during the 2 weeks of placebo treatment following paroxetine administration. These responses did not return to the rates observed in the initial placebo treatment prior to paroxetine administration. These effects could be attributed to the influence of receptor changes produced by paroxetine and continuing for at least 2 weeks following drug cessation. Previous studies assessing 5-HT receptor function suggest that 3 weeks of paroxetine treatment in this study would result in altered receptor function. Maj et al. (1996) demonstrated that 14 days of paroxetine administration to rats decreased density of 5-HT receptors and resulted in behavior changes that were consistent with decreased receptor function. Seventeen days of paroxetine administration to human volunteers, reduced $5HT_{1a}$ receptor function as measured by gepirone challenge test (Sargent et al. 1997). An SSRI treatment of depressed patients resulted in down regulation of $5HT_{1a}$ receptor activity as determined by ipsapirone challenge (Cowen 2000), and this down regulation has been linked to antidepressant action. Such down regulation of 5-HT receptors involves reductions in receptor density and protein synthesis, effects which would require time to reverse once SSRI administration had ceased (Saucier and Albert 1997). Therefore, we can speculate that paroxetine induced receptor changes persisted for at least 2 weeks following cessation of paroxetine administration, and were a factor in the continued suppression of aggressive and impulsive responses.

At another level of explanation, the decrease in impulsive responses during paroxetine treatment resulted in increased earnings for the subjects resulting from greater choices of the larger reward. These increased earnings may have sustained response choices in the post-treatment placebo condition independent of any biological changes. While entirely plausible, we offer two observations which are counter to such an interpretation: (1) the resulting changes in daily earnings for the subjects would be small, and (2) in previous acute drug studies we have observed decreases in impulsive choices which were not maintained during subsequent placebo sessions (Cherek and Lane 1999, 2000, 2001).

While we have observed changes in aggressive and impulsive responses following chronic paroxetine administration in CD subjects in this study, we cannot assume that results with non-CD subjects would be similar. We have observed differences in the effects of a 5-HT releaser *d*,*l*-fenfluramine on impulsive responses of CD subjects versus controls (Cherek and Lane 2000).

Future studies will determine if CD subjects have different response to drugs, which alter 5-HT function.

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