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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

### 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-

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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 Syva 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. Urinalysis 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.<sup>23</sup>

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 (Chamey 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