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GABAergic modulation of human social interaction in a prisoner's dilemma model via acute administration of alprazolam

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Abstract

Recent work in neuroeconomics has utilized game theory paradigms to examine neural systems that subserve human social interaction and decision making. Attempts to modify social interaction through pharmacological manipulation have been less common. Here we show dose-dependent modification of human social behavior in a prisoner's dilemma (PD) model following acute administration of the GABA-A modulating benzodiazepine alprazolam. Nine healthy adults received doses of placebo, 0.5, 1.0, and 2.0 mg alprazolam in a counterbalanced within-subject design, while completing multiple test blocks per day on an iterated PD game. During test blocks in which peak subjective effects of alprazolam were reported, cooperative choices were significantly decreased as a function of dose. Consistent with previous reports showing that high acute doses of GABA-modulating drugs are associated with violence and other antisocial behavior, our data suggest that at sufficiently high doses, alprazolam can decrease cooperation. These behavioral changes may be facilitated by changes in inhibitory control facilitated by GABA. Game theory paradigms may prove useful in behavioral pharmacology studies seeking to measure social interaction, and may help inform the emerging field of neuroeconomics.

Keywords

Alprazalom; Human; Social Behavior; Game Theory; Prisoner's Dilemma; Laboratory

Introduction

Studies of drug effects on human social behavior have taken many approaches, ranging from observational and observer rating techniques (Caldwell et al., 2004; Foltin et al., 1987; Knutson et al., 1998; Samson & Fromme, 1984; Ward et al., 1997) to experimentally-controlled tasks of cooperation and aggression with simulated other participants (Cherek et al., 2006; McCloskey & Berman, 2006; Spiga et al., 1994). With the advance of neuroimaging technologies, the rapidly growing field of neuroeconomics has embraced game theory models of human social interaction based upon experimental history and precise operational definitions (Krueger et al., 2008; Rilling et al., 2002; King-Casas et al., 2005), but relatively few have endeavored to alter social behavior via pharmacological modulation (e.g., Zak, 2008; Baumgartner, 2008). Thus, experiments in behavioral pharmacology that utilize game theory models to examine social behavior provide a convenient means for making direct contact with the neuroeconomics literature.

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Several decades ago, the prisoner's dilemma model was employed to examine a range of drug classes, and demonstrated that social behavior under this paradigm was acutely sensitive to drug effects (Hurst et al., 1969; Styx, 1974). More recently, investigators have utilized game theory models to demonstrate drug effects on prosocial behavior (e.g., cooperation, trust, fairness), including reboxetine (Tse and Bond, 2001) and oxytocin (Baumgartner et al., 2008; Kosfeld et al, 2005; Zak et al., 2007). Recent experiments employing a tryptophan depletion procedure demonstrated that temporary reduction of serotonin levels altered social behavior by increasing retaliation to unfair monetary offers in the ultimatum game (Crockett et al., 2008) and decreasing cooperative responding in the prisoner's dilemma game (Wood et al., 2006).

Based on extensive data suggesting that GABA-A modulating drugs can have untoward effects on social interaction, the present study sought to examine dose-related effects of alprazolam on human social behavior utilizing the prisoner's dilemma, a well-studied game theory paradigm that examines cooperative and non-cooperative behavior in a structured, competitive setting (Axelrod, 1984; Glimcher, 2003). Based on previous studies showing that high doses of benzodiazepines may facilitate aggression and other antisocial behaviors (Bond, 1998; Daderman et al., 2002), we expected to see decreases in cooperation at higher doses of alprazolam.

Methods

Subjects

This study was approved by the local IRB (UTHSC Committee for the Protection of Human Subjects). Male and female participants were recruited via local newspaper advertisements. Following telephone screening, potential participants came **to** the laboratory for more extensive psychiatric and medical interviews. Exclusionary criteria included: (a) current or past medical problems (e.g., seizures, diabetes, high blood pressure); (b) current use of any medications; (c) current illicit drug use (measured by daily urinalysis); (d) past substance dependence as defined by the Structured Clinical Interview for the DSM-IV (SCID-I, version 2.0, First et al., 1996) (e) history of any other DSM-IV Axis I disorder other than substance abuse; and (f) a body mass index ≥ 30, in order to avoid problems with drug distribution and elimination in obese individuals. For inclusion, subject must have had current recreational use of alcohol or benzodiazepines without meeting current DSM abuse or dependence criteria.

Prior to entering the study, subjects read and then signed a detailed consent form. Urine drug screen analysis with temperature monitoring and creatinine correction was carried out using enzyme multiple immunoassay (EMIT d.a.u ® - SYVA Corp) each day of participation. Participation was discontinued following drug-positive urine samples; one subject was discontinued for positive marijuana samples. Two additional subjects dropped out of the study without notification.

The final sample consisted of five men and four women with an average age (± SEM) of 23.56 (± 1.41) years, and an average of 12.44 (± 0.42) years of education completed. Race/ethnicity was comprised of seven African American, one Hispanic, and one Caucasian. As assessed by the Shipley Institute of Living Scale (Shipley-Boyle, 1967), the average age-adjusted t-score was 46.55 (± 2.81), with a WAIS equivalent of 102.33 (± 3.01). Past substance use, defined as more than three lifetime occasions, was as follows: alcohol (9), marijuana (5), benzodiazepine (2), cocaine (2), opiates (1).

Testing Protocol

Subjects participated either two or three days per week for approximately four weeks. On test days subjects arrived at approximately 08:00h. Breath CO and urine samples were collected at ≈ 8:15am. Subjects participated in four experimental test blocks lasting ≈ 45 min each. Test block 1 began at 08:30h. Following dose administration at 09:20 (see below), three more test blocks were completed at +40 min (10:00h), +220 min (13:00h) and +280 min (14:00h). Five minutes prior to each prisoner's dilemma test block, subjects completed the Addiction Research Center Inventory (ARCI) short form (Martin et al, 1971), a well-validated 49-item questionnaire measuring subjective drug effects. The PCAG (Pentobarbitol, Chlorpromazine, Alcohol Group) scale has proven to be a sensitive measure of subjective effects in many studies administering benzodiazepines (Lane et al., 2005, 2008; Rush & Griffiths, 1997). Subjects were paid for performance during experimental test blocks, with bonus payments for clean UA and BAC, attendance, and for completing the experiment.

Alprazolam Administration and Dosing Sequence

Placebo or alprazolam (Xanax, Pharmacia & Upjohn Co.) was given on each day of laboratory testing. Doses were administered orally and double-blind by a research assistant once per day at ≈09:25h, as described previously (Abreu & Griffiths, 1996; Lane et al., 2005). Placebo doses were composed of one #0 opaque capsule filled with corn starch. Active doses were identical to placebo but contained 0.5 mg, 1.0 mg, or 2.0 mg alprazolam. The order of active dose administration was counterbalanced across subjects.

Prisoner's Dilemma Task

This prisoner's dilemma (PD) represents perhaps the most widely studied model of strategic interaction, used to study reciprocal cooperation and non-cooperation, the latter sometimes referred to as exploitation or defection (Axelrod, 1984; Camerer, 2003). To assess acute drug effects, we utilized a modified, iterated version of the PD game in which players interacted repeatedly across multiple trials (described in complete detail in the Appendix material: https://xfiles.uth.tmc.edu/Users/slane/beh_pharm/). Subjects were presented with two response options labeled A and C on a custom-made response panel. Subjects were told that they were paired with other players during each trial block, and that these might be different people across the four daily experimental test blocks. Importantly, the instructional deception highlighted that each player may choose either A or C on any trial, and the probability of the computer's response (as well as the actual expected values on A and C) were unknown to the subject. In order to prevent biased responding based on (mis)interpretation of the instructions, the instructions were limited to the requirements of completing each trial and the basic payoff contingencies (instructions are provided in the Appendix material).

On each trial, the subject was presented the option of choosing either the letter A or C presented on the monitor screen, by pressing a corresponding button on a response panel. Once a choice was completed, the screen cleared and a stimulus array was presented showing the following information: "Your choice A/C," "Your outcome $X.XX" and "Other person's choice A/C," "Other person's outcome $X.XX." The game contingencies can be represented as a 2×2 matrix with four possible outcomes (see Figure in the Appendix). The choice of option A was defined as non-cooperative, the choice of option C was defined as cooperative. When both players chose option C (cooperative) both earned $0.25; when both players chose option A (non-cooperative) both lost $0.25; and when one chose C (cooperative) and the other chose A (non-cooperative), the non-cooperator earned $0.50 and the cooperator earned $0.

The "dilemma" of the PD game is that if both players could agree beforehand, they should agree to cooperate (option C) on every trial to maximize (group) earnings, but the temptation not to cooperate (option A) is always present because each player can maximize individual

earnings by defecting if the other continues to cooperate. When both do not cooperate, each ends up with the worst outcome. These operational definitions have been used in dozens of experimental studies over several decades (Axelrod, 1984; Camerer 2003). Technically, this is a modified variant of the PD game called the "hawk-dove" (Maynard-Smith, 1982), in which the choice of A and C have, on average, identical expected outcomes. These balanced payoff contingencies ensured that subjects' choices could not be a function of sensitivity to greater reward probability (average earnings) on one option, since each option (A or C) had an identical expected payoff value. Each test block lasted 100 rounds (i.e., trials). The balanced payoff contingency and the repeated-trials arrangement were utilized to enhance measurement of acute drug effects.

On every trial, the computer selected the A or C option at a probability of 0.50. Computer selections of C and A were random and stochastic, constrained within ± 0.10 of the 0.50 target. Over a 100-trial test block the obtained computer-selected probabilities of C and A could vary, but within an experimental day they always approached 0.50. Subjects completed four trial blocks over a 6-hour time period. Each trial block took approximately 45 minutes to complete, providing a sufficient window of opportunity to capture peak drugs effects.

Dependent Measures and Data Analyses

The primary dependent variable of interest was the number of choices for the cooperative response option (the C button). Behavioral data were calculated as a difference score between test block 1 (pre-administration) and the test block of peak behavioral effects, measured as a corresponding change in both behavior on the PD task and subjective effects on the PCAG-ARCI scale administered immediately before the PD task. Analysis of behavioral and subjective effects data across the entire experiment day revealed too much variability across subjects to provide significant outcomes (see Appendix material). Peak effects were selected based on graphical inspection of the data. The comparative placebo data were taken from the placebo dose that immediately preceded each of the the three active doses, corresponding to the exact same test block in which the peak effect was observed for the active dose. For example, if placebo was given on Day 4 and 1.0 mg on Day 5, and the peak behavioral (PD task) and ARCI-PCAG effect was observed in test block 2, then the respective placebo dose was taken from test block 2 on Day 4. This was repeated for all three doses. The majority of peak effects occurred in test block 2 or 3, where peak concentrations of alprazolam would be expected (Greenblatt & Wright, 1993): test block 2 (29.6%), test block 3 (59.3%), test block four (11.1%). Primary statistical analyses involved one-way ANOVA with repeated measures across dose. Tukey post-hoc comparisons (alpha = .05) were used to further examine significant main effects and interactions. Sample sizes were too small for an appropriate gender analysis.

Results

Figure 1 (top panel) shows the effect of placebo and the three alprazolam doses on the cooperative response data. Cooperative responding decreased systematically as a function of dose: $F(3, 24) = 4.23$, $p < 0.02$ with Huynh-Feldt correction. Tukey HSD follow-up tests revealed that the 2.0 mg dose was significantly different than placebo and 0.5 mg. Figure 1 (bottom panel) shows the ARCI-PCAG data. Scores increased from pre-dose levels as a function of dose: $F(3, 24) = 5.26$, $p < 0.01$ with Huynh-Feldt correction. Tukey HSD follow-up tests revealed that the 1.0 mg and 2.0 mg doses were both significantly different than placebo. No other ARCI scales revealed significant effects. Results of mean cooperative and ARCI-PCAG data across all four tests blocks are provided in the Appendix material.

Discussion

Alprazolam decreased operationally-defined cooperative responses at 2 mg, relative to placebo and 0.5 mg. The decrease in cooperation supports previous studies from naturalistic settings showing that benzodiazepine misuse is associated with a variety of maladaptive social behaviors (Bond, 1998; Daderman et al., 2002; Galvan et al., 2000). The 2 mg dose is a relatively high acute dose for individuals who are not using benzodiazepines or alcohol on a daily basis or in large quantities. Therefore, these outcomes may represent behavior patterns corresponding to recreational misuse or abuse on benzodiazepines, rather than therapeutically effective doses (Lane et al., 2008; Mintzer & Griffiths, 2005; Woods & Winger, 1997). Regular benzodiazepine users would likely have greater tolerance, and the observed effect on cooperation may be substantially diminished. More broadly however, the data are consistent with laboratory and epidemiological studies demonstrating that moderate to high doses of GABA-A modulating drugs (including alcohol), can engender aggression and other antisocial behaviors (Bond, 1998; Miczek et al, 2003).

While the use of a game theory paradigm and peak effects data analysis strategy were intended to achieve strong internal validity, these approaches are not without limitations. For example, the changes in cooperative responding were transient, and only observable under a peak effects analysis. The variability in test performance across all experimental test sessions hinders evidence of a drug effect beyond the first two hours after administration. This may be due to the pharmacokinetics of alprazolam, or limitations in the use of this prisoner's dilemma procedure for repeated measurement across longer time periods. The prisoner's dilemma model has been applied to a broad range of phenomenon in the social and economic sciences (Dugatkin, 1999). However, it is unclear to what extent changes in cooperative behavior observed in this study generalize to forms of maladaptive social behavior described in clinical and epidemiological reports. Thus, the external validity of the data may be considered limited at present.

This report aims to reinforce the utility of employing game theory paradigms in psychopharmacology (Stix, 1974; Tse & Bond, 2001; Zak et al., 2007; Crocket et al., 2008), in order to (a) isolate key factors that may further understanding of drug effects on human social behavior, and (b) make use of established paradigms and measures of important social behaviors such as cooperation, exploitation, trust, and generosity. Future studies might employ multiple game theory paradigms within the same experiment to explore more systematically individual drug classes and neurotransmitter systems, in order to characterize drug effects on a range of human social behaviors.

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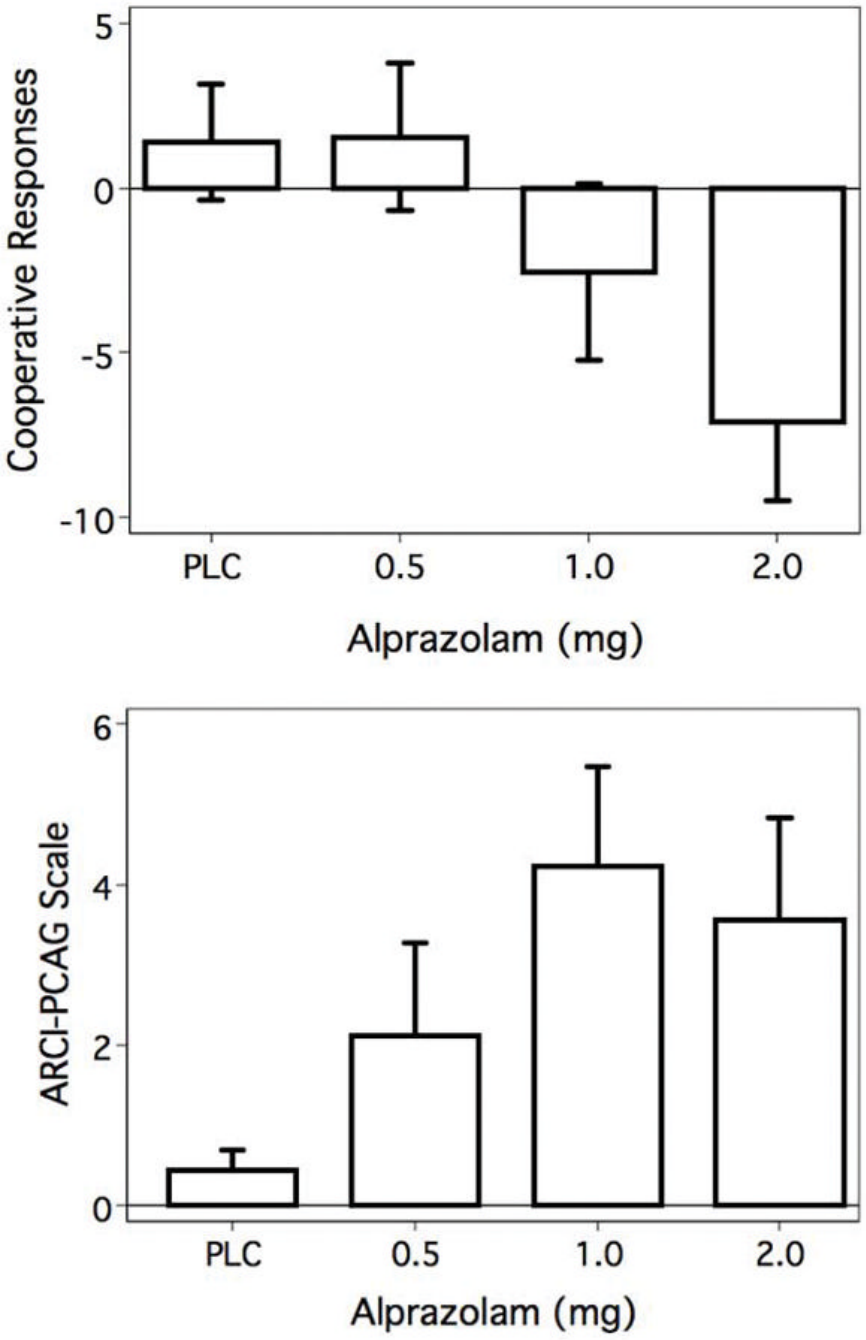

Figure 1.

Peak effect data plotted as means and standard errors for the cooperative responses (top panel) and the PCAG scale of the Addiction Research Center Inventory (PCAG-ARCI, bottom panel). **Cooperative response and PCAG-ARCI data were calculated as a difference score between test block 1 (pre-dose) and test block in which the peak dose effect occurred.**