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Effects of amphetamine, morphine, and CP 55,940 on Go/No-Go task performance in rhesus monkeys

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Abstract

In humans, impulsivity measured as false alarms in a Go/No-Go task is reportedly decreased by amphetamine and is not affected by oxycodone and delta(9)-tetrahydrocannabinol (THC). To model these findings in animals, three rhesus monkeys were trained to perform a food-reinforced Go/No-Go task. In this task, amphetamine decreased false alarms (i.e., responding during No-Go trials), but only at doses that also decreased hits (i.e., responding during Go trials). Morphine generally decreased hits but not false alarms. The cannabinoid (CB) receptor agonist CP 55,940 decreased both false alarms and hits, but only at doses that also decreased the number of trials completed. Additional studies in animals and humans are necessary to delineate the conditions under which amphetamine and other psychoactive drugs affect impulsivity in Go/No-Go tasks.

Keywords

amphetamine; morphine; CP 55,940; impulsivity; Go/No-Go task; rhesus monkeys

Introduction

Impulsivity is closely linked to drug abuse (de Wit, 2008). The present study is part of an effort to develop procedures suitable to investigate drug effects on impulsivity in nonhumans. Here, a Go/No-Go procedure was used to examine drug effects on behavioral inhibition. In humans, acute administration of amphetamine decreases several measures of impulsivity, including false alarms in a Go/No-Go task (de Wit et al., 2002). In contrast, the opioid oxycodone does not alter measures of impulsivity in humans (Zacny and de Wit, 2009). Delta(9)-tetrahydrocannabinol increases some measures of impulsivity (i.e., response inhibition in a stop task) but not others (e.g., Go/No-Go task performance) in humans (McDonald et al., 2003). To determine whether these findings can be modeled in nonhumans, the present study examined effects of amphetamine, morphine, and the CB receptor agonist CP 55,940 on Go/No-Go task performance in rhesus monkeys.

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Conflicts of Interest: There are no conflicts of interest.

Method

Subjects

One male (KI) and two female (HE, JA) adult rhesus monkeys were maintained at a constant weight by receiving food pellets during sessions and primate chow and fruit in the home cage (with free access to water), in accordance with local IACUC and NIH guidelines. For further details, see Bai et al. (2011).

Apparatus

During sessions, monkeys were seated in chairs placed in operant chambers equipped with two levers, two lights, and a food pellet receptacle, controlled by MED-PC software. For further details, see Bai et al. (2011).

Procedure

During daily sessions, which began with a 15 min time out in the operant chamber, monkeys were trained to lever press for food in a self-paced discrete trial Go/No-Go procedure. A trial began by illumination of the light above one lever. A response on that lever extinguished that light and illuminated the other light that flashed for a maximum of 0.8 s at 15 Hz (Go signal) or slower (No-Go signal; KI: 10Hz; HE, JA: 7.5 Hz). Correct responses (i.e., a response on the second lever during a Go trial, not responding on the second lever during the 0.8 s No-Go trial) extinguished the second light, delivered a food pellet, and started a 5 s intertrial interval. Incorrect responses (i.e., not responding during a Go trial, responding during a No-Go trial) ended the trial without delivering a food pellet and initiated a 10 s time-out before the 5 s intertrial interval started. The session ended after 100 Go trials and 100 No-Go trials (in random order, but with at most 4 consecutive trials of the same type) or after 45 min, whichever occurred first. A response on the second lever was designated a hit during Go trials and a false alarm during No-Go trials; training continued until the percentages of hits and false alarms attained stable (as defined by Schoenfeld et al., 1956) high and low levels, respectively. Animals were testable if both hits and false alarms differed by less than 10% between two consecutive saline control sessions. All doses of each drug were tested first in an ascending order and then in a random order. Amphetamine tests were completed before morphine tests began, and CP 55,940 tests were conducted last.

Drugs

Morphine sulfate (Research Technology Branch, NIDA, Rockville, MD) and d-amphetamine sulfate (Sigma-Aldrich Co., St. Louis, MI) were dissolved in sterile water; CP 55,940 (Sigma-Aldrich Co.) was dissolved in a 1:1:18 mixture of absolute ethanol, emulphor-620, and 0.9% saline. All drugs were injected s.c. (0.2 – 1.5 ml) immediately before sessions, except CP 55,940, which was injected 45 min before sessions. Doses were expressed as the weight of the salt.

Data analysis

For each drug test, the proportions of hits and false alarms were used to calculate the sensitivity index SI and the response bias index RI (see Koek et al., 1984), and frequency

distributions yielded modal and mean response latencies. Deviations of the mean from the mode have been used to examine effects of amphetamine on long reaction times that are thought to constitute lapses of attention (see Acheson and de Wit, 2008; de Wit 2008). Test results were considered drug effects if a dose produced, on both tests, results outside the range observed during the saline sessions conducted 24 h before each test.

Results

At the highest dose tested, amphetamine decreased false alarms in KI and JA but increased false alarms in HE, and decreased hits in all three monkeys (Fig. 1, left panels). Morphine decreased hits in all three monkeys, increased false alarms in KI, and decreased false alarms in JA (middle panels). CP 55,940 decreased both hits and false alarms, but only at doses that decreased the number of trials completed. The combined effects on hits and false alarms of each of the three drugs decreased SI, indicating decreased sensitivity, and yielded RI values smaller than 0, indicating an increased bias not to respond (Fig. 2). Under vehicle control conditions, the means of the observing response latencies were generally higher than their modes (Table 1). Amphetamine increased this difference, as did morphine and CP 55,940. Amphetamine increased the mean Go response latency but not its mode at the higher dose tested in HE and JA, whereas morphine and CP 55,940 did not consistently alter Go response latencies (data not shown).

Discussion

In humans, amphetamine decreased false alarms without having significant effects on performance during Go trials, suggesting decreased impulsivity (de Wit et al., 2002). In a reaction time task in humans, amphetamine decreased the reaction time mean more than the mode, indicating a decrease of long reaction times thought to constitute lapses of attention (Acheson and de Wit, 2008). Similar evidence that amphetamine decreased impulsivity and decreased lapses of attention was not obtained in the present study in rhesus monkeys. Instead, amphetamine affected false alarms only at doses that also affected responding during Go trials (i.e., hits), reflecting a general bias towards not responding, and amphetamine increased reaction times. The current results are consistent with findings that amphetamine and methamphetamine decrease responding of mice in Go/No-Go tasks while having no effects specific to response inhibition during No-Go trials (Loos et al., 2010; Moschak et al., 2012). In these latter studies, trials were not initiated by an observing response, like the aforementioned study in humans (de Wit et al., 2002), but unlike the present study. Thus, a stimulant-induced general reduction of responding does not appear to be specific to the “self-paced” Go/No-Go task used here.

The present study failed to find consistent effects of morphine on false alarms. These data are consistent with those from human subjects in which oxycodone and THC did not significantly affect Go/No-Go task performance (Zacny and de Wit, 2009; McDonald et al., 2003). Unlike the studies in humans, morphine decreased responding by rhesus monkeys primarily during Go trials in the present experiments, and the CB agonist CP 55,940 decreased responding during Go and on No-Go trials at doses that decreased the number of trials completed. This could be due to procedural differences, as responding during Go trials

is generally very accurate in human Go/No-Go studies (e.g., Zacny and de Wit, 2009; McDonald et al., 2003). In contrast, the percentage correct responses during Go trials (“hits”) in the present studies varied between 70 and 100%. Overall, the present data strongly suggest that additional studies in animals and humans are necessary to delineate conditions under which amphetamine and other psychoactive drugs selectively affect false alarms in Go/No-Go tasks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Effects of amphetamine (left panels), morphine (middle panels), and CP 55,940 (right panels) on responding during Go trials (hits) and responding during No-Go trials (false alarms) in a Go/No-Go task by three monkeys (upper panels: KI; middle panels: HE, lower panels, JA). Horizontal gray bars indicate the range of saline values: upper bars represent percentage hits; lower bars represent percentage false alarms. Each dose was tested twice. Numbers between parentheses indicate the mean percentage of trials completed; if absent, all 200 trials were completed during both tests.

Figure 2.

Effects of amphetamine (left panels), morphine (middle panels), and CP 55,940 (right panels) on signal detection indices of sensitivity [SI] and response bias [RI] during Go/No-Go task performance of three monkeys (upper panels: KI; middle panels: HE, lower panels, JA). Horizontal gray bars indicate the range of saline values: upper bars represent SI; lower bars represent RI. Each dose was tested twice.