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Self-administration of cocaine-antihistamine combinations: Super-additive reinforcing effects

Zhixia Wang and **William L. Woolverton**
Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS

Abstract

Histamine H_1 receptor antagonists have some behavioral effects that predict abuse liability. In the present study, diphenhydramine and cocaine each maintained i.v. self-administration under a progressive-ratio schedule in rhesus monkeys. When cocaine and DPH were combined in a 1:1 ratio of the ED_{50}s, the combination was super-additive in all monkeys. The data predict that the combination of cocaine and histamine H_1 receptor antagonists would have enhanced potential for abuse relative to either drug alone.

Keywords

cocaine; diphenhydramine; drugs interaction

In preclinical models, histamine H_1 receptor antagonists can have effects that are associated with abuse liability. Monkeys will self-administer some H_1 receptor antagonists (Beardsley and Balster, 1992), and H_1 receptor antagonists can have amphetamine-like discriminative stimulus effects (Evans and Johanson, 1989). In humans, H_1 receptor antagonists tend to be sedative (Weiler et al., 2000). Abuse has not been particularly problematic, and the compounds are available over the counter. However, the antihistamine tripelennamine has been abused in a mixture with the opioid partial agonist pentazocine ("Ts and Blues"; Shannon and Su, 1982). The present study was designed to examine the possibility of an interaction between cocaine and the H_1 receptor antagonist diphenhydramine (DPH) as positive reinforcers.

The experiments were approved by the University of Mississippi Medical Center's Animal Care and Use Committee and in accordance with National Institutes of Health Guidelines. Subjects were four male rhesus monkeys (*Macaca mulatta*, 10.4–11.3 kg). Each was implanted with an i.v. silastic catheter under isoflurane anesthesia. In baseline sessions, cocaine (0.1 or 0.2 mg/kg/injection) or saline was available as a consequence of lever pressing under a progressive-ratio (PR) schedule of reinforcement (see Wilcox et al., 2000). When responding was stable, test sessions were added to the daily sequence between two saline and two cocaine sessions. After every second test session, a randomly determined cocaine or saline was conducted. In test sessions, a dose of cocaine (0.03–0.3mg/kg/injection), DPH (0.1–3.0 mg/kg/injection) or the cocaine-DPH combination in a 1:1 ratio of the individual ED_{50}s (total dose

Corresponding author: Zhixia Wang, M.D., Department of Psychiatry, University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216, Email: Zwang@psychiatry.umsmed.edu, Phone: 601-815-1287, FAX: 601-984-5899.

0.04–0.8 mg/kg/injection) was available under conditions identical to baseline sessions. Doses were tested at least twice, once each with a saline or cocaine session the day before.

The mean number of injections per session was calculated individually from the test sessions. ED_{50} values were calculated individually using the ascending limb of log dose-response functions and non-linear regression analysis (GraphPad Prism 4.0). Predicted additive dose-response functions of the cocaine-DPH combination were calculated and statistically compared to the experimentally-determined cocaine-DPH effects using ANOVA test (PharmToolsPro 1.1.27; The McCary Group, Inc.). The interaction index, defined as the ratio of experimentally-determined dose combinations to the predicted additive combinations (Z_{mix}/Z_{add}; Tallarida, 2000), were calculated at levels of 6, 8, 10 and 12 injections/session. An interaction index significantly less than 1.0 indicates super-additivity.

Cocaine and DPH functioned as reinforcers in a dose-dependent manner in all monkeys. For cocaine, the mean maximum injections/session (± S.E.M.) was 19.1 (± 0.4) and the ED_{50} was 0.062 (± 0.005 mg/kg/inj). For DPH, the mean maximum injections/session was 11.9 (± 1.6) and the ED_{50} was 0.51 (± 0.12 mg/kg/inj). The dose-response function for combinations of cocaine:DPH was to the left of the function predicted by additivity in all monkeys (Figure 1). The interaction indexes at 6, 8, 10, and 12 injections/session level were 0.42 (± 0.08), 0.38 (± 0.07), 0.35 (± 0.08) and 0.33 (± 0.09) respectively ($P < 0.05$ at all levels).

Consistent with previous research, both cocaine and DPH served as i.v. positive reinforcers in monkeys. That cocaine maintained more responding than DPH under a PR schedule extends previous findings to suggest that DPH is a weaker reinforcer than cocaine, consistent with lower liability for abuse. When cocaine and DPH were combined they were super-additive with regard to potency. Maximum responding maintained by the combination, a measure of reinforcing strength, was also higher than predicted by addivity and comparable to that of cocaine alone. Since both cocaine and the combination approximated the 20-injection maximum for the assay, additional research will be required to establish whether the two can differ in strength. In any case, the present results suggest that cocaine and H_1-antihistamines can be synergistic in terms of reinforcing effects and that the combination may have significant potential for abuse.

The reinforcing effects of cocaine seem to involve increased dopamine neurotransmission in the brain. Histamine H_1 receptor antagonists increase dopamine levels in the neostriatum and nucleus accumbens (Dringenberg et al., 1998) and block histamine–induced excitation GABAergic cells, indirectly inhibiting dopamine neurons (Korotkova et al., 2002). It is possible, that dopaminergic actions are involved in the reinforcing effect of the combination. However, additional research will also be required to establish the mechanism of the cocaine-antihistamine interaction.

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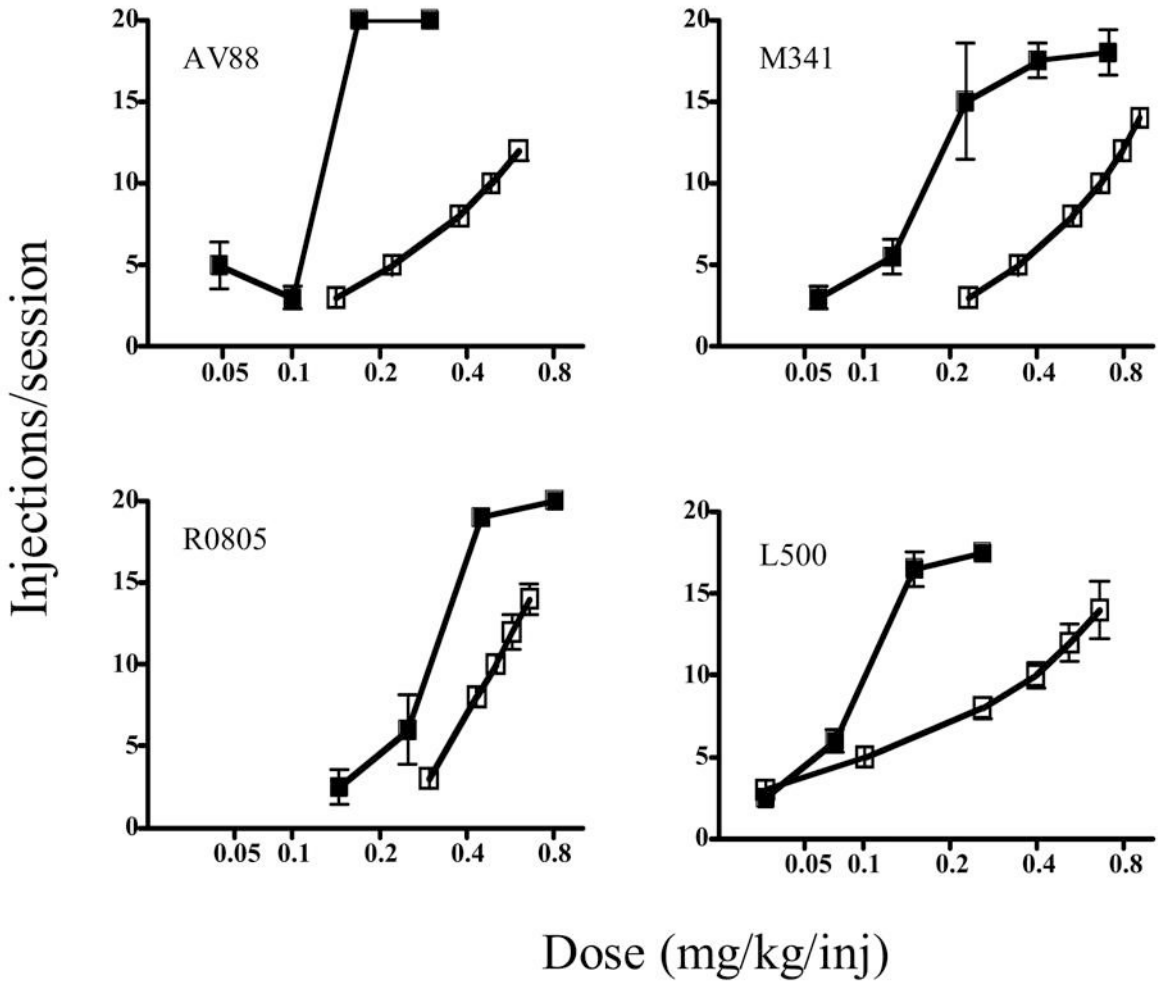

Fig. 1.

Dose-response curves of self-administration of cocaine/DPH combinations for individual monkeys under a progressive-ratio schedule of reinforcement. Solid squares represent experimentally-determined effects of cocaine/DPH combinations; open squares are effects of dose combinations predicted by additivity. Vertical lines are S.E.M. Doses are the total dose of cocaine+DPH. Numbers in panels are monkey identification numbers.