Effects of the Kappa Agonist U69,593 on Naltrexone’s Discriminative Stimulus Effect in Subjects Given Chronic, Intermittent Sucrose Access
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Introduction
• Naltrexone (NTX) is a non-specific opioid antagonist that is comparable to naloxone (Narcan).
• Avena, Hoebel & colleagues (2004) demonstrated that rats given access to a chronic, intermittent sucrose solution have increased endorphin function.
• Our previous research has shown that rats given access to a 25% sucrose solution can discriminate NTX (0.1 mg/kg - 3.2 mg/kg) from saline in an operant procedure.
• We wondered if NTX’s discriminative stimulus effects are mediated by kappa-opioid receptors. To examine this, we used U69,593, a kappa-opioid receptor agonist in multiple discrimination testing procedures.

Method
• Seven male Sprague Dawley Rats trained daily using a two-choice operant chamber (Med-Associates). Subjects were housed under 12-hour dark /12-hour light conditions (lights on at 6:00 AM). Subjects were given sucrose access during the dark cycle and had water access during the light cycle.
• One hour after sucrose access, subjects were injected with saline or their training dose of NTX. Discrimination training began 15 minutes later. Left lever presses were reinforced following NTX administration and right lever presses were punished with a timeout. Under saline conditions contingencies were reversed. Discrimination training conditions were assigned in quasi-random order.
• Acquisition was defined as criteria performance (80% correct responses) achieved for 8 of 10 daily sessions.

Acquisition
• Seven subjects acquired the discrimination in a mean of 85 sessions (Figure A).

Reversal Test
• Reversal tests were conducted to determine if U69,593 alters NTX’s discriminative stimulus effects. Subjects were injected with a training dose of NTX followed by a single dose of U69,593 (0.001 mg/kg - 0.1 mg/kg, s.c.) following by increasing doses of NTX (0.032 mg kg - 10.0 mg/kg, s.c.). Expected graphs for both Kappa mediated and not Kappa mediated dose effect curves are shown (Figure C & D).

Cumulative Dosing
• A cumulative dosing procedure was used to determine if U69,593 alters the ability of NTX to produce its discriminative stimulus effects. Subjects were injected with U69,593 (0.01 mg/kg - 0.1 mg/kg, s.c.) followed by increasing doses of NTX (0.032 mg kg - 10.0 mg/kg, s.c.). Expected graphs for both Kappa mediated and not Kappa mediated dose effect curves are shown (Figure C & D).

Discussion
• U69,593 produced a rightward shift in the NTX cumulative dose effect curve in subjects that showed an increase in NTX’s potency to produce training-dose-appropriate responding. U69,593 did not appear to alter NTX’s rate suppressing effects.
• An increase in the potency of NTX to produce its discriminative stimulus effects was observed in some subjects.
• Reversal tests indicate that U69,593 did not alter the established NTX discriminative stimulus effects.
• Currently, we are testing the ability of U69,593 to alter NTX’s discriminative stimulus effects before subjects develop an increased sensitivity to NTX.

Sensitivity
• Consistent with previous research done by Schindler and colleagues (1993) and France and Woods (1985 & 1987) chronic administration of NTX can increase NTX’s potency in producing discriminative stimulus effects.

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