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Role of opioidergic mechanisms and GABA uptake inhibition in the heroin-induced discriminative stimulus effects in rats

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Abstract:
The present study was designed to investigate the involvement of opioidergic component as well as to study GABAergic mechanisms in the expression of heroin discrimination. Male Wistar rats were trained to discriminate heroin (0.5 mg/kg, *ip*) from saline (*ip*) in a two-choice water reinforced fixed ratio (FR) 20 drug discrimination paradigm. In substitution tests, heroin (0.0625–0.5 mg/kg) and morphine (0.5–2 mg/kg, *ip*) evoked a dose-dependent generalization for the drug lever-responding, while muscimol (1 mg/kg, *ip*, a $GABA_A$ receptor agonist) produced a weak partial substitution (ca. 48% heroin-lever responding). Neither tiagabine (2.5 mg/kg, *ip*; a GABA reuptake inhibitor), vigabatrin (75–150 mg/kg, *ip*; an irreversible inhibitor of GABA transaminase), nor baclofen (0.5 mg/kg, *ip*; a $GABA_B$ receptor agonist) substituted for heroin. In combination studies, the stimulus effects produced by heroin (0.5 mg/kg) or morphine (2 mg/kg) were dose-dependently blocked by opioid receptor antagonists naltrexone (0.1–1 mg/kg, *ip*), and naloxone (0.5–1 mg/kg, *ip*). The peripherally-acting naloxone methiodide at a dose of 1 mg/kg, *ip* did not alter, while at a dose of 10 mg/kg that penetrates across the blood-brain barrier, it reduced the stimulus effects of heroin or morphine. Pretreatment with tiagabine (2.5–5 mg/kg) produced a rightward shift of a heroin dose-response curve, while vigabatrin (75–300 mg/kg), baclofen (0.5–2.5 mg/kg) or muscimol (0.5–2 mg/kg) given prior to heroin (0.0625–0.5 mg/kg) failed to alter heroin discrimination. Our findings confirm previous studies on the significance of μ-opioidergic mechanisms in the expression of heroin discrimination and add the observation that selective inhibition of GABA reuptake, but not inhibition of GABA transaminase or direct stimulation of $GABA_A$ and $GABA_B$ receptors, can decrease the overall effects of heroin.

Key words:
heroin, opioid receptors, GABA, discriminative stimulus