DOES COMBINED TREATMENT WITH NOVEL ANTI-DEPRESSANTS AND A DOPAMINE D₃ RECEPTOR AGONIST REPRODUCE COCAINE DISCRIMINATION IN RATS?

Ma³gorzata Filip, Iwona Papla

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smütra 12, PL 31-343 Kraków, Poland


It is established that dopamine (DA) neurotransmission plays a critical role in the behavioral (e.g. discriminative stimulus) effects of cocaine in rodents. Nonetheless, research has also demonstrated that reciprocal signaling between DA and monoamine neurotransmitters, i.e. serotonin (5-HT) and norepinephrine (NE) has important implication for understanding the actions of cocaine. The present study was focussed on the ability of novel antidepressant drugs (milnacipram, reboxetine and venlafaxine), which affect either NE or both 5-HT and NE reuptake mechanism, to alter (enhance or antagonize) the discriminative stimulus effects of cocaine. Moreover, we investigated if the combined treatment with those drugs and a DA D₃ receptor agonist (pramipexole) could reproduce cocaine discrimination. Male Wistar rats were trained to discriminate cocaine (10 mg/kg, ip) from saline (ip) in a two-choice, water-reinforced fixed-ratio 20 drug discrimination paradigm. Given alone, none of antidepressant drugs induced substitution for the cocaine-lever responses. Pramipexole (0.25 mg/kg) produced a partial substitution for cocaine (i.e. 43–52% cocaine-lever responding). In combination experiments, milnacipram (10 mg/kg) or reboxetine (10 mg/kg) given with submaximal doses of cocaine (1.25–5 mg/kg) did not affect the cocaine dose-response curve or its ED₉₀ values. Venlafaxine (10 mg/kg) given in combination with submaximal doses of cocaine (0.6–5 mg/kg) produced significant enhancement of cocaine discrimination with a leftward shift in the cocaine dose-response curve and a decrease in its ED₉₀ value. Pretreatment with either milnacipram (10 mg/kg) or reboxetine (10 mg/kg) failed to modulate the partial substitution evoked by pramipexole (0.25 mg/kg). On the other hand, venlafaxine (10 mg/kg) given in combination with a submaximal dose of pramipexole (0.25 mg/kg), which separately elicited 16 and 42% the cocaine-lever responses, produced significant enhancement of cocaine discrimination (up to 99% of the drug-lever responding). These results indicate that the discriminative stimulus effects of cocaine in rats can be enhanced by venlafaxine or mimicked by the combination with this antidepressant drug and the DA D₃ receptor agonist. This finding, together with the recent data reporting the lack of rewarding properties of venlafaxine and the attenuation of morphine dependence and withdrawal signs in rats by the drug, may indicate a possible therapeutic use of this antidepressant in cocaine abuse.

Key words: cocaine, milnacipram, pramipexole, reboxetine, venlafaxine, discriminative stimulus effects, rats