Simultaneus agonism at NOP and antagonism at KOP receptors reduce cocaine self-administration: a potential mechanism for the effect of buprenorphine on cocaine seeking

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Buprenorphine, approved for opioid dependence, possesses agonist activity to MOP, DOP and NOP receptors and act as antagonist to KOP receptor. Recent evidence showed potential efficacy of this drug in the treatment of cocaine dependence (Mooney et al., 2013). However, the mechanism at the basis of this effect is not clear. Here we tested the effect of a NOP antagonist (compound A) and a NOP agonist (Ro 64-6198) alone or in combination with a KOP antagonist (compound B) on cocaine self-administration. Wistar rat were trained to self-administer cocaine sessions (250 μg/infusion, FR5, 2 h) until they reached a stable baseline. On test days rats were administered with NOP agonist Ro 64-6198 (0, 1, 3 mg/kg/2ml), NOP antagonist compound A (0, 3, 30 mg/kg/3ml) and KOP antagonist (0, 1, 3, 9 mg/kg/2ml), or administered with combination of either NOP agonist Ro 64-6198 (1 mg/kg/ml) and KOP antagonist (3 mg/kg/2ml).

Results showed that single treatment with NOP agonist, NOP antagonist or KOP antagonist alone had no effect on cocaine self-administration. However, when the NOP agonist (Ro 64-6198) and KOP antagonist (compound B) were given together they significantly ($t = 2.230$, $df = 18$, $^*p<0.05$) reduced cocaine self-adminstration. Inactive control lever was not affected by drug treatment.

These findings show that cocaine self-administration can be attenuated by concomitant activation of NOP and inactivation of KOP receptors. Selective modulation of these receptors do not appear to be able to modify cocaine intake. Based on this finding it is tempting to speculate that buprenorphine reduces cocaine consumption by simultaneously activating NOP and inhibiting KOP receptors.

Mooney et al. (2013). Contemp Clin Trials. 34(2):196-204.