

# Reduction of Cocaine Consumption by Buprenorphine Requires Concomitant Activation of NOP and MOP Opioid Receptor

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Buprenorphine has been clinically used for heroin addiction treatment. Promising evidence shows potential effects also on cocaine abuse. However, the mechanism through which it attenuates cocaine consumption remains to be elucidated. Buprenorphine is a partial agonist at MOP and NOP and an antagonist at KOP and DOP opioid receptors. We hypothesize the its MOP and NOP agonist activities may be involved in the reduction of cocaine intake. Here, we explored this hypothesis using drug self-administration paradigms. Results showed that buprenorphine (0.3, 1 and, 3.0 mg/kg) given intraperitoneally (IP) 90 min before access to cocaine significantly and dose dependently reduced cocaine use. Pretreatment with the preferential but not selective MOP, antagonist naltrexone or with the selective NOP antagonist SB-612111 did not prevent buprenorphine-induced reduction of cocaine intake. However, when naltrexone and SB-612111 were combined, the effect of buprenorphine on cocaine was completely reversed. To confirm that co-activation of MOP and NOP receptors is the underlying mechanism through which buprenorphine inhibits cocaine consumption, we tested another two compounds, namely AT-034, and AT-201, which had a range of affinity and intrinsic activity profiles for MOP and NOP receptors, but weak ability to affect KOP transmission. Consistent with our hypothesis based on buprenorphine's effects, results demonstrated that AT-034 and AT-201, which co-activate MOP and NOP receptors, attenuated cocaine self-administration, comparison to buprenorphine. These effects were specific for cocaine since the same treatments did not show the same effects on saccharin self-administration at any of the dose tested. Taken together, our data demonstrate that for buprenorphine, co-activation of MOP and NOP receptors is essential to lower cocaine consumption. These results open new vistas on the treatment of cocaine addiction by developing compounds with mixed MOP/NOP agonist properties.