

DISSERTATION ABSTRACT

DOPAMINE D1 AND D3 RECEPTOR POLYPHARMACOLOGY IN COCAINE  
REWARD AND COCAINE SEEKING

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*Background:* In the search for efficacious pharmacotherapies to treat cocaine addiction much attention has been given to agents targeting D1 or D3 receptors because of the involvement of these receptors in cocaine-related behaviors. D1 and D3 receptor partial agonists and antagonists have been shown to reduce cocaine reward, reinstatement of cocaine seeking and conditioned place preference (CPP) in rodents and non-human primates. However, translation of these encouraging results with selective D1 or D3 receptor agents has been limited due to a number of factors including toxicity, poor pharmacokinetic properties and extrapyramidal and sedative side effects.

*Purpose:* Given the role of D1 and D3 receptors in cocaine-related behaviors and the urgent need for effective anti-cocaine treatments, it is important that we continue to pursue new pharmacological approaches such as the combinations of compounds that have differential functions at multiple dopamine receptors. The aims of this dissertation were to evaluate the effects of the novel strategy of simultaneous treatments with a D3 receptor antagonist (NGB 2904) and D1 receptor partial agonist (SKF 77434) in animal models of drug addiction, including cue-induced reinstatement of cocaine seeking, cocaine conditioned place preference (CPP) and cocaine self-administration in rats.

*Methods:* In the reinstatement experiment, rats underwent cocaine self-administration training followed by extinction and a cue-induced reinstatement test. Prior to the reinstatement test rats were treated with one of several doses of NGB 2904, SKF 77434 or the combination of the two and their lever presses were measured. In the CPP experiment rats were conditioned to experience cocaine in one compartment of a CPP apparatus and saline in the other. After conditioning rats were treated with the same

compounds alone or combined prior to the CPP test. The time spent in the cocaine-paired compartment prior to and after conditioning was measured as an indication of cocaine CPP. In the self-administration experiment, rats were trained to self-administer cocaine under a progressive ratio (PR) schedule of reinforcement. After demonstrating stable baseline break points (BPs) rats were treated repeatedly with NGB 2904 or SKF 77434 alone or the combination of the two.

*Results:* The co-administration of NGB 2904 and SKF 77434, at doses which when administered individually produced no significant effects, prior to reinstatement or CPP tests significantly reduced lever pressing and time spent in the cocaine-paired environment, suggesting synergistic effects of the combined compounds on their abilities to reduce cocaine seeking. When administered to rats self-administering cocaine under a PR schedule of reinforcement doses of NGB 2904 which were ineffective alone significantly potentiated the break point-reducing effects of SKF 77434.

*Conclusions:* The results of this study indicate that the combined treatment with a D1 receptor partial agonist and D3 receptor antagonist produces robust decreases in cocaine seeking and reward. These effects provide insight into a novel therapeutic approach to treat cocaine addiction.