MODULATION OF COCAINE-LIKE BEHAVIOURAL ACTIVITY BY SEROTONIN UPTAKE INHIBITION RELATIVE TO THE EFFECTS OF THE NOVEL AND SELECTIVE DOPAMINE TRANSPORTER INHIBITOR, D-84

A dissertation submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

By

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<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
<tr>
<td>% CLR</td>
<td>% Cocaine Lever Responding</td>
</tr>
<tr>
<td>% DLR</td>
<td>% Drug Lever Responding</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>C</td>
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<td>CI</td>
<td>Confidence Intervals</td>
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<td>Centimeter</td>
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<td>Dopamine</td>
</tr>
<tr>
<td>DAT</td>
<td>Dopamine Uptake Transporter</td>
</tr>
<tr>
<td>ED</td>
<td>Effective dose 50%</td>
</tr>
<tr>
<td>FR</td>
<td>Fixed Ratio</td>
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<td>First Fixed Ratio</td>
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<tr>
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<td>Intraperitoneal</td>
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<tr>
<td>mg/kg</td>
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</tr>
<tr>
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<tr>
<td>NA</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>NET</td>
<td>Noradrenaline Uptake Transporter</td>
</tr>
<tr>
<td>NAc</td>
<td>Nucleus Accumbens</td>
</tr>
<tr>
<td>VTA</td>
<td>Ventral Tegmental Area</td>
</tr>
<tr>
<td>PFc</td>
<td>Prefrontal Cortex</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of Mean</td>
</tr>
<tr>
<td>SERT</td>
<td>Serotonin Uptake Inhibitor</td>
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ABSTRACT

MODULATION OF COCAINE-LIKE BEHAVIOURAL ACTIVITY BY SEROTONIN UPTAKE INHIBITION RELATIVE TO THE EFFECTS OF THE NOVEL AND SELECTIVE DOPAMINE TRANSPORTER INHIBITOR, D-84.

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Cocaine dependence is a major health concern worldwide, but despite this high rate of abuse there are currently no approved therapies for cocaine dependence. Replacement pharmacotherapies are one possible approach for treating cocaine dependence, and identification of such therapeutics for cocaine abuse is the long-term goal of this research. Cocaine binds to, and inhibits uptake at the dopamine (DAT), serotonergic (SERT) and noradrenaline (NET) uptake transporters, but studies have shown that cocaine produces its
strong behavioural and positive reinforcing effects through inhibition of the DAT. To this end a great number of diverse, non-selective DAT-inhibiting compounds have been investigated as potential cocaine replacement therapies. It was the initial objective of this research to determine whether the behavioral profile of a novel, selective DAT inhibitor, D-84, fit with that thought for an ideal cocaine replacement therapy. Results indicated that D-84 stimulated locomotor activity, incompletely generalized to the cocaine cue in discrimination tests, attenuated cocaine-self-administration and was self-administered. These observations provide a profile consistent, although perhaps not ideal, with one possible treatment strategy for cocaine dependence.

Although it is well established that cocaine predominantly produces its abuse-related effects through inhibition of the DAT, recent evidence suggests that inhibition at the SERT may have modulating effects on the pharmacology of cocaine-like compounds. The second part of this dissertation investigated what effects that increasing SERT inhibition had on the cocaine-like behavioural effects of DAT inhibitors, as a method of determining the fruitfulness of incorporating this feature into future drug candidates to improve them. RTI-55 (DAT Ki 2.7 nM SERT Ki 3 nM) and GBR-12909 (DAT Ki 4.3 nM SERT Ki 73 nM) were selected based on their high and intermediate SERT inhibitory effects, respectively. They were compared in behavioural studies with D-84, which is considered to be a selective DAT inhibitor. The results indicated that although increasing SERT inhibition attenuated locomotor activity effects, it had less effect on cocaine-like discriminative stimulus and reinforcing effects, at least with the doses tested.

**Key Words:** DAT inhibitor, SERT inhibition, Cocaine Dependence, Reinforcing effects, Self-administration, Discrimination