

This document only includes an excerpt of the corresponding thesis or dissertation. To request a digital scan of the full text, please contact the Ruth Lilly Medical Library's Interlibrary Loan Department (rlmlill@iu.edu).

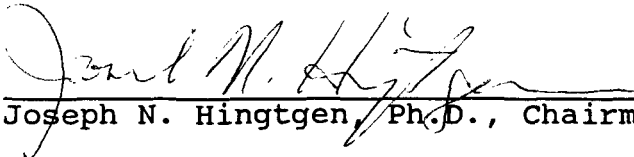
PHARMACOKINETIC AND NEUROCHEMICAL CORRELATES
OF CONTEXT-DEPENDENT BEHAVIORAL SENSITIZATION

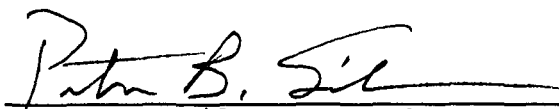
Peter Lawrence Bonate

Submitted to the faculty of the University Graduate School
in partial fulfillment of the requirements
for the degree
Doctor of Philosophy
in the Department of Medical Neurobiology
Indiana University

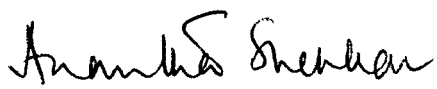
December, 1996

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.


Joseph N. Hingtgen, Ph.D., Chairman


Peter B. Silverman, Ph.D., Co-Chair

Doctoral
Committee


Anantha Shekhar, M.D., Ph.D.

August 20, 1996

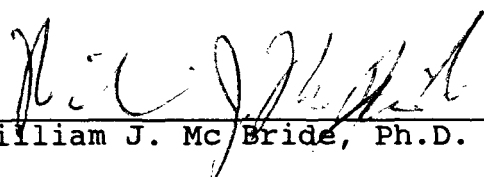

William J. McBride, Ph.D.

TABLE OF CONTENTS

ACCEPTANCE PAGE.....	iii
COPYRIGHT.....	iv
ACKNOWLEDGMENTS.....	iv
INDEX TO FIGURES.....	ix
INDEX TO TABLES.....	xi
ABSTRACT.....	xii
INTRODUCTION.....	1
Proposed Mechanisms of Sensitization	5
Context-Dependent Sensitization and Sensitization as a Conditioning Process.....	6
Drug Redistribution Theory of Sensitization.....	18
Neurochemical Theory of Sensitization.....	25
Dopaminergic Alterations in Sensitization	26
Synthesis, Storage, and Metabolism.....	26
Dopamine Release.....	26
Dopaminergic Impulse Flow.....	31
Postsynaptic Dopamine Receptors.....	31
Dopamine Autoreceptors.....	33
Summary of Dopaminergic Alterations and Integration with Context-Dependent Sensitization.....	36
EXPERIMENTAL DESIGN, RATIONALE, AND OBJECTIVES.....	41
HPLC Analysis of Cocaine in Brain and Plasma	45
Brain Cocaine Distribution After Multiple Dose Administration	47
Cocaine Context-Dependent Sensitization	48
Cross-Sensitization between Psychostimulants	48

EXPERIMENTAL PROCEDURES.....	49
Materials and Common Methods	49
Reagents and Standards.....	49
Animals.....	50
Behavioral Assessment.....	50
Brain Dissection.....	51
HPLC Analysis of Cocaine in Brain and Plasma	51
Instrumentation and Data Analysis.....	51
Sample Preparation.....	52
HPLC Conditions.....	54
HPLC Analysis of Neurotransmitters	55
Sample Preparation.....	55
HPLC Conditions, Instrumentation, and Data Analysis.....	55
Brain Cocaine Distribution After Multiple Dose Administration	56
Experimental Design.....	57
Statistical Analysis.....	58
Cocaine Context-Dependent Sensitization Protocol	58
Experimental Design.....	59
Pharmacokinetic Analysis.....	60
Statistical Analysis.....	63
Cross-Sensitization between Psychostimulants	64
Experimental Design.....	64
Statistical Analysis.....	65

RESULTS.....	67
HPLC Analysis of Cocaine in Brain and Plasma	67
Brain Cocaine Distribution After Multiple Dose Administration	76
Cross-Sensitization between Psychostimulants	96
DISCUSSION.....	102
HPLC Analysis of Cocaine in Brain and Plasma	102
Brain Cocaine Distribution After Multiple Dose Administration	105
Cocaine Context-Dependent Sensitization	107
Cross-Sensitization between Psychostimulants	117
CONCLUSIONS.....	121
REFERENCES.....	124
CURRICULUM VITAE.....	142

ABSTRACT

Peter Lawrence Bonate

Pharmacokinetic and Neurochemical Correlates of
Context-Dependent Behavioral Sensitization

Repeated, intermittent psychostimulant administration results in sensitization, an increased behavioral response to subsequent drug administration. The mechanisms underlying sensitization are not understood. Previous research has shown that following repeated, intermittent cocaine or amphetamine administration, brain drug levels are elevated compared to animals administered a single equimolar dose. Thus, sensitization may be the result of altered drug distribution upon repeated administration. Psychostimulant-induced sensitization has also been shown to be context-dependent and to demonstrate cross-sensitization between psychostimulants. Using cocaine as the test drug, the purpose of this study was to determine whether cocaine levels are altered in a context-dependent manner and if cocaine levels are altered in context-dependent cross-sensitization.

A reversed phase HPLC assay using ultraviolet detection was developed for cocaine analysis in biological matrices. In a 1-day context-dependent sensitization

paradigm, rats previously administered cocaine in the testing cage had increased locomotor activity, decreased striatal cocaine clearance, and increased striatal volume of distribution following cocaine challenge compared to saline controls and animals administered cocaine in their home cage. Behavioral differences between groups were greatest immediately following drug administration, whereas pharmacokinetic differences were not apparent until later time periods. No difference in plasma cocaine concentration, striatal dopamine content, or striatal dopamine metabolite content was observed among groups.

Cross-sensitization between cocaine and amphetamine was also found to be context-dependent. Animals administered 0.75 mg/kg amphetamine daily for 8 days demonstrated context-dependent sensitization following cocaine challenge. There was no difference in striatal cocaine content or plasma cocaine levels. These results suggest that context-dependent sensitization is independent of brain cocaine levels and is due to other processes.