Antidepressant-like effects of

3,4-methylenedioxymethamphetamine

(MDMA, ecstasy)

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Table of Contents

List of Tables ........................................................................................................... viii

List of Figures .......................................................................................................... ix

Abstract .................................................................................................................... xi

Declaration .............................................................................................................. xiii

Acknowledgments ................................................................................................... xv

Abbreviations .......................................................................................................... xvii

Chapter 1. Background .......................................................................................... 1

1.1. MDMA: an overview ...................................................................................... 1

1.2. Pharmacology of MDMA .............................................................................. 6

  1.2.1. Pharmacokinetics and metabolism of MDMA ............................................ 6

  1.2.2. The pharmacological action of MDMA in the brain ..................................... 12

1.3. Immediate effects of MDMA in humans ...................................................... 15

  1.3.1. Psychological MDMA effects ..................................................................... 15

  1.3.2. Tolerance to the subjective effects of MDMA ............................................. 18

  1.3.3. Physiological and side effects of MDMA ................................................. 20

1.4. The subacute (rebound) effects of MDMA .................................................... 23

1.5. Long-term effects of MDMA .......................................................................... 26

1.6. Depression: an overview ............................................................................. 31

  1.6.1. Definition .................................................................................................... 31

  1.6.2. Mechanisms of development of the depressive symptoms ........................ 33

    1.6.2.1. Monoaminergic hypothesis of depression .............................................. 34

    1.6.2.1.1. Serotonergic system in depression ................................................. 34

Irina Majumder, PhD thesis 2010
1.6.2.1.2. Noradrenergic system in depression ................................................................. 36
1.6.2.1.3. Dopaminergic system in depression ........................................................................ 38
1.6.2.2. Cholinergic system in depression .............................................................................. 38
1.6.2.3. Role of the hypothalamo-pituitary adrenal axis and cytokines in depression .......... 39
1.6.2.4. Role of GABA and neuropeptides in depression ...................................................... 41
1.6.2.5. Neurotrophic hypothesis of depression ....................................................................... 42
1.6.3. Mechanisms of action of clinically prescribed antidepressants .................................. 43
1.6.4. Genetics of depression .................................................................................................. 45
1.6.5. Depression as a comorbidity or a side effect of drugs .................................................. 48

1.7. Preclinical studies of depression ...................................................................................... 49
1.7.1. Overview of the animal models of depression ............................................................... 49
1.7.2. Neurochemical models of depression .......................................................................... 53
1.7.3. Environmental and social stress-induced models of depression .................................. 54
  1.7.3.1. Learned Helplessness ............................................................................................... 54
  1.7.3.2. Chronic Mild Stress ................................................................................................. 55
  1.7.3.3. Social stress and maternal separation models ......................................................... 58
1.7.4. Olfactory bulbectomy .................................................................................................. 61
1.7.5. Animal tests of depression .......................................................................................... 61
  1.7.5.1. Tail Suspension Test ............................................................................................... 62
  1.7.5.2. Forced Swimming Test ............................................................................................ 62
  1.7.5.3. Sucrose preference test ........................................................................................... 65
1.7.6. Genetic rodent models of depression .......................................................................... 67
  1.7.6.1. Fawn-Hooded rats ................................................................................................. 67
  1.7.6.2. Wistar Kyoto rats .................................................................................................. 70
  1.7.6.3. Flinders Sensitive Line rats .................................................................................... 71

1.8. MDMA and depression: what are the links? ................................................................. 76

1.9. Summary, aims and hypotheses ...................................................................................... 82

Irina Majumder, PhD thesis 2010
Chapter 2. Effects of MDMA on behaviour in an animal model of depression........ 87

2.1. Introduction..............................................................................................................87

2.2. Materials and methods ..........................................................................................90

2.2.1. Animals.....................................................................................................................90

2.2.2. Drugs ........................................................................................................................91

2.2.3. Experimental protocol.............................................................................................91

2.2.3.1. Weighing of animals............................................................................................ 91

2.2.3.2. Preparation and administration of drugs.............................................................. 92

2.2.3.3. Injections schedule............................................................................................. 92

2.2.3.4. Forced Swimming Test ......................................................................................... 93

2.2.3.5. Sucrose preference test ....................................................................................... 94

2.2.3.6. Locomotor activity assessment .......................................................................... 95

2.2.3.6.1. Equipment ....................................................................................................... 95

2.2.3.6.2. Experimental protocol ..................................................................................... 95

2.2.4. Statistical analysis .................................................................................................. 96

2.3. Results......................................................................................................................96

2.3.1. Weight......................................................................................................................96

2.3.2. Locomotor activity ................................................................................................. 98

2.3.3. Forced Swimming Test ......................................................................................... 99

2.3.4. Sucrose preference test ......................................................................................... 101

2.4. Discussion............................................................................................................... 103

Chapter 3. Pharmacokinetics of MDMA in an animal model of depression ............ 110

3.1. Introduction............................................................................................................ 110

3.2. Animals and methods ............................................................................................ 111

3.2.1. Animals...................................................................................................................111

3.2.2. Drug preparation and administration ................................................................. 112
Chapter 4. Effects of repeated administration of MDMA on the cortical levels of 5-HT and 5-HIAA in an animal model of depression

4.1. Introduction

4.2. Animals and methods

4.2.1. Animals, drugs and experimental protocol

4.2.2. Measurement of 5-HT and 5-HIAA levels in cortex

4.2.3. Statistical analysis

4.3. Results

4.4. Discussion

Chapter 5. Effects of MDMA on mood in subjects with and without a predisposition to depression

5.1. Introduction

5.2. Subjects and methods

5.2.1. Subjects

5.2.2. Recruitment

5.2.2.1. Inclusion criteria

5.2.2.2. Exclusion criteria

5.2.3. Study testing schedule

5.2.3.1. Baseline session

5.2.3.2. Party session
5.2.4. Demographic data ......................................................................................................132
5.2.5. Psychological assessment .....................................................................................133
  5.2.5.1. Brief Symptom Inventory (BSI) ................................................................. 133
  5.2.5.2. Beck Depression Inventory (BDI) ............................................................... 134
  5.2.5.3. Profile of Mood States (POMS) ................................................................. 135
5.2.6. MDMA and nicotine exposure .............................................................................135
5.2.7. Statistical analysis ...............................................................................................136

5.3. Results ......................................................................................................................137
  5.3.1. Demographic data ...............................................................................................137
  5.3.2. MDMA and nicotine exposure ...........................................................................142
  5.3.3. Use of ecstasy and other substances at the party session .....................................143
  5.3.4. Psychological tests .............................................................................................144
    5.3.4.1. Brief Symptom Inventory ................................................................. 144
    5.3.4.2. Profile of Mood States ............................................................................ 146
      5.3.4.2.1. Total Mood Disturbance score ...................................................... 146
      5.3.4.2.2. Tension/Anxiety scale ................................................................. 147
      5.3.4.2.3. Depression/Dejection scale .......................................................... 150
      5.3.4.2.4. Anger/Hostility scale ................................................................. 150
      5.3.4.2.5. Vigour/Activity scale ................................................................. 150
      5.3.4.2.6. Fatigue/Inertia scale ................................................................. 151
      5.3.4.2.7. Confusion/Bewilderment scale .................................................... 151
    5.3.4.3. Beck Depression Inventory ........................................................................ 151
  5.3.5. Correlational analysis ........................................................................................ 152

5.4. Discussion .................................................................................................................155

Chapter 6. Effects of MDMA on serotonergic function in users with and without a
predisposition to depression ......................................................................................... 168
  6.1. Introduction .......................................................................................................... 168

Irina Majumder, PhD thesis 2010
7.3.2.1. Brief Symptom Inventory ................................................................. 188
7.3.2.2. Beck Depression Inventory............................................................. 189
7.3.2.3. Profile of Mood States................................................................. 189

7.4. Discussion .......................................................................................... 192

Chapter 8. Conclusion .................................................................................. 197
8.1. Summary of findings ............................................................................. 197
8.2. Limitations of the study ......................................................................... 201
8.3. Future directions ...................................................................................... 204

References ................................................................................................. 207

Appendix 1. Publications in support of the thesis ............................................. 243
Publications ................................................................................................. 243
Conference papers ....................................................................................... 243
List of Tables

TABLE 3.1. PHARMACOKINETIC AND METABOLIC CHARACTERISTICS OF MDMA AND MDA IN SD AND FSL RATS................................................................................................................. 114

TABLE 5.1. DEMOGRAPHIC DATA OF SUBJECTS WITH AND WITHOUT A PREDISPOSITION TO DEPRESSION .................................................................................................................................. 138

TABLE 5.2. ECSTASY USE BY SUBJECTS WITH AND WITHOUT A PREDISPOSITION TO DEPRESSION ........ 139

TABLE 5.3. MINIMUM AND MAXIMUM VALUES FOR ECSTASY USE PARAMETERS............................................. 139

TABLE 5.4. LIFETIME AND CURRENT USE OF OTHER ILLICIT DRUGS BY SUBJECTS WITH AND WITHOUT A PREDISPOSITION TO DEPRESSION ................................................................................... 140

TABLE 5.5. BRIEF SYMPTOM INVENTORY T-SCORES ......................................................................................... 145

TABLE 7.1. DEMOGRAPHIC DATA DISTRIBUTION BETWEEN GROUPS WITH DIFFERENT ECSTASY EXPOSURE ................................................................................................................................. 187

TABLE 7.2. BSI T-SCORES REPORTED BY ECSTASY USERS WITH DIFFERENT EXPOSURE TO THE DRUG ..... 188
List of Figures

FIGURE 1.1 CHEMICAL STRUCTURES OF AMPHETAMINE, METHAMPHETAMINE, MDMA AND MESCALINE 1

FIGURE 1.2. METABOLIC PATHWAYS OF MDMA .......................................................... 9

FIGURE 2.1. MEAN WEIGHT OF SD AND FSL RATS IN TREATMENT GROUPS THROUGHOUT THE
EXPERIMENTAL PERIOD .................................................................................................... 97

FIGURE 2.2. MEAN TOTAL PEAK AREAS FOR THE LOCOMOTOR ACTIVITY TIME-RESPONSE CURVES OF SD AND FSL RATS IN THE SALINE, MDMA10 AND METH2 TREATMENT GROUPS AFTER DRUG ADMINISTRATION ........................................................................................................ 98

FIGURE 2.3. TOTAL IMMOBILITY TIME IN THE FST AFTER ACUTE AND REPEATED DRUG ADMINISTRATION ............................................................................................................................. 100

FIGURE 2.4. CONSUMPTION OF THE 32% SUCROSE SOLUTION BY SD AND FSL RATS IN THE SALINE, MDMA5, MDMA10 AND METH2 TREATMENT GROUPS ........................................................... 102

FIGURE 3.1. MDMA AND MDA CONCENTRATIONS IN CORTEX AND WHOLE BLOOD SAMPLES IN SD AND FSL RATS ............................................................................................................................................. 113

FIGURE 4.1. 5-HT AND 5-HIAA LEVELS IN THE CORTEX OF SD AND FSL RATS AFTER THREE WEEKS OF TREATMENT ............................................................................................................. 120

FIGURE 5.1. BRIEF SYMPTOM INVENTORY RESULTS ............................................................................ 144

FIGURE 5.2. PROFILE OF MOOD STATES TOTAL MOOD DISTURBANCE SCORES AT THE BASELINE AND PARTY SESSIONS ........................................................................................................................... 147

FIGURE 5.3. PROFILE OF MOOD STATE SCALES SCORES AT THE BASELINE SESSION .................... 148

FIGURE 5.4. PROFILE OF MOOD STATE SCALES SCORES AT THE PARTY SESSION .......................... 149

FIGURE 5.5. BECK DEPRESSION INVENTORY SCORES ........................................................................... 152

Irina Majumder, PhD thesis 2010
FIGURE 6.1. THE 5-HT UPTAKE IN PLATELETS IN SUBJECTS WITH AND WITHOUT A PREDISPOSITION TO DEPRESSION ............................................................................................................. 176

FIGURE 7.1. PROFILE OF MOOD STATES TOTAL MOOD DISTURBANCE SCORES IN THE GROUPS WITH DIFFERENT ECSTASY EXPOSURE ............................................................................................................. 190

FIGURE 7.2. PROFILE OF MOOD STATES DEPRESSION/DEJECTION SCORES IN THE GROUPS WITH DIFFERENT ECSTASY EXPOSURE ............................................................................................................. 191
Abstract

3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is a popular club drug that is abused worldwide. The main subjective effects of the drug include enhanced mood and self-esteem. Due to these effects, ecstasy may be used at higher rates by people with pre-existing mood disorders, or a predisposition to depression, in order to ‘self-medicate’ their state. This, in turn, may lead to more regular drug use, and, hence, a higher risk of side effects and negative impact on health. Moreover, some mechanisms of MDMA action in the brain are similar to those of clinically prescribed antidepressants, as the drug primarily affects the serotonin (5-HT) system. This suggests that the drug may have antidepressant-like activity.

The studies reported here, both preclinical and clinical, were designed to investigate possible antidepressant-like effects of MDMA in subjects with a predisposition to depression.

In the animal study, the effects of MDMA following single and repeated administration were compared between Sprague-Dawley and the Flinders Sensitive Line rat strains, the latter being a putative model of depression. The drug’s effects on behaviour were assessed in the Forced Swimming Test, which is widely used to detect the depressive-like state in laboratory animals. Acute MDMA administration had a dose-dependent antidepressant-like effect that was more evident in the Flinders Sensitive Line animals. This effect was diminished following 3 weeks of repeated drug injection, possibly due to the development of tolerance. The chosen dosing regime didn’t affect the cortical levels of 5-HT and its metabolite.
40 current ecstasy users participated in the clinical study. Predisposition to depression was assessed using a questionnaire (Brief Symptom Inventory) that determines the rates of distress in various psychological spheres. Mood scores and depressive symptoms were assessed when participants were drug-free and when they attended a social gathering. Twenty participants, with and without a predisposition to depression, who voluntarily chose to take a pill at a social gathering, were assessed 1 hour after drug consumption, and the mood disturbance and depressive symptoms were compared with participants who abstained from pill consumption. Ecstasy users with a predisposition to depression reported higher mood disturbance and more prominent depressive symptoms when they were not under the influence of the drug. At the party, mood was improved in all participants irrespective of whether they chose to consume a pill, whereas subjects predisposed to depression reported a relative decrease in depressive symptoms only after pill consumption, which may be considered as an antidepressant-like effect of the drug. Certain variants of the 5-HT transporter gene polymorphism were associated with higher depressive scores.

Analysis of the effects of different previous ecstasy exposure revealed that subjects with a greater number of pills consumed in their lifetime report more prominent positive effects following ecstasy consumption, which may explain their more frequent use.

In sum, an immediate antidepressant-like effect of MDMA was evident both in an animal model of depression and in users predisposed to depression. This may suggest the self-medicating potential of MDMA in subjects with a predisposition to depression.
Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Irina Majumder and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Irina Majumder
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Abbreviations

0°C – degrees Celsius

14C – radioactive carbon isotope

3α,5α-THP – 3α,5α-tetrahydroprogesterone

5-HIAA – 5-hydroxyindoleacetic acid

5-HT – serotonin (5-hydroxytryptamine)

5-HTT – serotonin transporter

5-HTTLPR – serotonin transporter linked polymorphic region

8-OH-DPAT – 8-hydroxy-2-(di-n-propylamino)tetralin

ACTH – adrenocorticotropic hormone

AMPT – alpha-methylparatyrosine

ANOVA – analysis of variance

AUC – area under the curve

BDI – Beck Depression Inventory

BDNF – brain-derived neurotrophic factor

BSI – Brief Symptom Inventory

cAMP – cyclic adenosine monophosphate

CBF – cerebral blood flow

CH3OH – methanol

CH3COONa - sodium acetate

Ci – curie

cm – centimetre
Cmax – peak concentration
CNS – central nervous system
COMT – catechol-O-methyltransferase
CREB – cAMP response element binding
CRF – corticotropin-releasing factor
CSF – cerebrospinal fluid
CYP – cytochrome P450
DA – dopamine
DAT – dopamine transporter
DFP – diisopropyl fluorophosphate
dGTP – deoxyguanosine triphosphate
DMT – dimethyltryptamine
DNA – deoxyribonucleic acid
dNTP – deoxyribonucleoside 5'-triphosphate
DOPAC – 3,4-dihydroxyphenylacetic acid
DSM-IV – Diagnostic and statistical manual of mental disorders (IV edition)
EDTA – ethylenediaminetetraacetic acid
FH – Fawn-Hooded
FRL – Flinders Resistant Line
FSL – Flinders Sensitive Line
FST – Forced Swimming Test
g – gram
GABA – gamma-aminobutyric acid
GHB – gamma-hydroxybutyric acid

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h – hour
HHA – 3,4-dihydroxyamphetamine
HHMA – 3,4-dihydroxymethamphetamine
HMA – 4-hydroxy-3-methoxyamphetamine
HMMA – 4-hydroxy-3-methoxymethamphetamine
HPA – hypothalamo-pituitary axis
HPLC – high performance liquid chromatography
HPLC-ECD – high performance liquid chromatography with electrochemical detection
HVA – homovanillic acid
i.p. – intraperitoneal
IFN-α – interferon-alpha
IL – interleukin
IMVS – Institute of Medical and Veterinary Science
kg – kilogram
LC-MS – liquid chromatography mass spectrometry
LMM – Linear Mixed Model
LSD – lysergic acid diethylamide
M – mol/litre
MAO – monoamine oxidase
MAOI – monoamine oxidase inhibitor
MDA – 3,4-methylenedioxyamphetamine
MDD – major depressive disorder
MDEA – 3,4-methylenedioxyethylamphetamine
MDMA – (±)-3,4-methylenedioxyamphetamine (ecstasy)
METH – methamphetamine
mg – milligram
MHPG – 3-methoxy-4-hydroxyphenylglycol
min – minute
ml – millilitre
mm – millimetre
mRNA – messenger ribonucleic acid
nA – nanoamper
NA – noradrenaline
NaCl – sodium chloride
NaH₂PO₄ – sodium dihydrogen phosphate
NAT – noradrenaline transporter
ng – nanogram
NMe5-HT – N-methyl-serotonin
NPY – neuropeptide Y
OSA – octanesulphonic acid
p.o. – per os
PBS – phosphate buffered saline
PCA – perchloric acid
PCR – polymerase chain reaction
PMA – para-methoxyamphetamine
POMS – Profile of Mood States
PPP – platelet-poor plasma
PRP – platelet-rich plasma
PTSD – posttraumatic stress disorder
REM – rapid eye movement
RM – Repeated Measures
ROS – reactive oxygen species
s – second
SCL-90 – Symptom Checklist-90
SD – Sprague-Dawley
SEM – standard error of mean
SMH – self-medication hypothesis
SNRI – serotonin-noradrenaline reuptake inhibitor
SSRI – selective serotonin reuptake inhibitor
T½ – half-life
TBE – tris/borate/EDTA
TCA – tricyclic antidepressant
TH – tyrosine hydroxylase
Tmax – time when peak concentration is reached
TMD – Total Mood Disturbance
TNFα – Tissue Necrosis Factor alpha
TPH – tryptophan hydroxylase
Trp – tryptophan
U – unit
V – volt
VMAT₂ – vesicular monoamine transporter type 2
VNTR – variable-number-tandem-repeat
VTA – ventral tegmental area

WKY – Wistar Kyoto

y – year

μl – microlitre