Antidepressant-like effects of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)

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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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Abbreviations

^{0}C – degrees Celsius

^{14}C – 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

CH_3OH – methanol

CH_3COONa - sodium acetate

Ci – curie

cm – centimetre

C_{max} – 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

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-methylenedioxymethamphetamine (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

NaH_2PO_4 – 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

$VMAT_2$ – vesicular monoamine transporter type 2

VNTR – variable-number-tandem-repeat

VTA – ventral tegmental area

WKY – Wistar Kyoto

y – year

µl – microlitre