The use of combined telemetry and microdialysis techniques to assess 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') effects in rats

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Thesis Abstract

3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') is known to produce hyperthermia and adverse cardiovascular effects in humans following consumption, which can be life threatening. In animals, MDMA also produces similar effects as seen in humans such as increase in core body temperature (Tc) which has been linked to chronic neurotoxicity. Currently, clinical treatment of these adverse effects is inadequate mainly due to limited understanding of the mechanism involved in the acute MDMA-induced adverse effects. Due to ethical reasons, MDMA studies in humans are limited and studies have relied on the use of animal models to investigate MDMA effects. Therefore, it is important to assess MDMA-induced effects using appropriate techniques to relate the findings from animals to humans.

The general aims of this thesis were to investigate effects of different methods used to measure core body temperature and behaviour following MDMA administration and the validity of combined telemetry and microdialysis techniques to assess MDMA and its active metabolite, 3,4-methylenedioxyamphetamine (MDA) effects on body temperature (Tc), behaviour, heart rate (HR), locomotor activity (LMA), and 5-HT extracellular levels in the rat striatum.

The first part of this thesis looked at the influence of methodological approaches used to assess changes in core body temperature and behaviour following MDMA administration. A number of studies used rectal probe measurement which requires handling and restraining of rats which results in confounding effects on the parameters measured including Tc and behaviour. Telemetry has been developed to measure these behavioural parameters without the necessity of handling the rats. The use of rectal probe caused potentiation of 10mg/kg (i.p.) MDMA-induced increase in core body temperature

compared to the use of telemetry to measure Tc during the first 60 minutes following MDMA administration and has also resulted in a lower survival rate. These results demonstrate the importance of using appropriate techniques when measuring these parameters to avoid confounding effects and that telemetry provides a more accurate assessment of MDMA-induced change in core body temperature.

The second part of the thesis looked at the validity of combined telemetry and microdialysis techniques to investigate effects of systemic administration of MDMA and central administration of MDMA and MDA on Tc, HR, LMA and 5-HT extracellular levels in the striatum. Systemic administration of 10mg/kg (i.p.) MDMA produced significant increase in Tc, HR, LMA and 5-HT extracellular levels in the striatum whereas central administration of 100μM MDMA only produced significant increase in 5-HT extracellular levels. Central administration of 5μM MDA produced no significant changes in the parameters measured, which suggests that MDA, at concentration used in this study, does not play a major role in MDMA-induced increase in 5-HT extracellular levels in the striatum and the occurrence of hyperthermia.

In summary, this thesis has demonstrated that a combined telemetry and microdialysis technique provides a better approach to assess MDMA effects in rats, allowing central administration of drugs, and simultaneous measurement of physiological and neurochemical parameters. The combined techniques provided a better tool to investigate the effects of MDMA particularly looking at the relationship between the physiological and neurochemical effects in animal models.

Declaration

I, Intan Sofia Omar certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary institution 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

°C – degree Celcius

4-MTA – 4-methylthioamphetamine

5-HIAA – 5-hydroxyindoleacetic acid

5-HT – serotonin (5-hydroxytryptamine)

aCSF – artificial cerebrospinal fluid

ANOVA – analysis of variance

AUC – area under the curve

CH_3OH – methanol

cm – centimetre

C_{max} – peak concentration

COMT – catechol *O*-methyl transferase

CYP – cytochrome P450

DA – dopamine

DOB – 2,5-dimethoxy-4-bromoamphetamine

DOPAC – 3,4-dihydroxyphenylacetic acid

EDTA – ethylenediaminetetraacetic acid

g – gram

h – hour

HHA – 3,4-dihydroxyamphetamine

HHMA – 3,4-dihydroxymethamphetamine

HMA – 4-hydroxy-3-methoxyamphetamine

HMMA – 4-hydroxy-3-methoxymethamphetamine

HPLC – high performance liquid chromatography

HPLC-ED – high performance liquid chromatography with electrochemical detection

i.m. – intramuscular

i.p. – intraperitoneal

kg – kilogram

M – mol/litre

MAO – monoamine oxidase

MAOI – monoamine oxidase inhibitor

MDA – 3,4-methylenedioxyamphetamine

MDE – 3,4-methylenedioxyethylamphetamine

MDMA – 3,4-methylenedioxymethamphetamine (Ecstasy)

METH – methamphetamine

mg – miligram

min – minute

ml – mililitre

mm – milimitre

NaCl – sodium chloride

NaH_2PO_4 – sodium dihydrogen phosphate

OSA – octanesulphonic acid

PMA – para-methoxyamphetamine

s – second

SD – Sprague-Dawley

SEM – standard error of mean

V – volt

μl – microlitre