

E is for Ecstasy by Nicholas Saunders  
Appendix 4: Bibliography

Biochemistry

Elayan, I., Gibb, J.W., Hanson, G.R., Lim, H.K., Foltz, R.L. and Johnson, M. , Short-term Effects of 2,4,5-Trihydroxyamphetamine, 2,4,5-Trihydroxymethamphetamine and 3,4-Dihydroxymethamphetamine on Central Tryptophan Hydroxylase Acticity. *J. Pharm. Exptl. Therap.* 262 813-8 (1993).

The short term effects of the three title metabolites of MDMA (THA, THM and DHM) on tryptophan hydroxylase are reported. The first two metabolites were quite effective, but the third (DHM) had no effect. In vitro studies were unsuccessful in reversing these changes.

Gibb, J.W., Hanson, G.R. and Johnson, M. Effects of (+)-3,4-Methylenedioxymethamphetamine [(+)-MDMA] and (-)-3,4-Methylenedioxymethamphetamine [(-)-MDMA] on Brain Dopamine, Serotonin, and their Biosynthetic Enzymes. *Soc. Neurosciences Abstrts.* 12 169.2 (1986).

The optical isomers of MDMA were studied in rats, as to the extent of serotonin and dopamine depletion, and the changes in their respective biosynthetic enzymes TPH (tryptophane hydroxylase) and TH (tyrosine hydroxylase). The (+) was the more effective in reducing serotonin levels at several sites in the brain, and was the more effective in reducing the TPH levels at all sites. Striatal TH was not effected by either isomer.

Hanson, G.R., Hanson, G.R. and Johnson, M. Effects of (+)-3,4-Methylenedioxymethamphetamine [(+)-MDMA] and (-)-3,4-Methylenedioxymethamphetamine [(-)-MDMA] on Brain Dopamine, Serotonin, and their Biosynthetic Enzymes. *Soc. Neurosciences Abstrts.* 12 169.2 (1986).

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Hanson, G.R., Merchant, K.M., Johnson, M., Letter, A.A., Bush, L. and Gibb, J.W. Effect of MDMA-like Drugs on CNS Neuropeptide Systems. *The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA.* Kluwer, New York. (1990) Ed: S.J. Peroutka.

An increase in both neurotensin and dynorphin in selected areas of rat brain following single administrations of MDMA has been observed. The ramifications of these changes are discussed.

Johnson, M., Bush, L.G., Stone, D.M., Hanson, G.R. and Gibb, J.W. Effects of Adrenalectomy on the 3,4-Methylenedioxymethamphetamine (MDMA)-induced Decrease of Tryptophan Hydroxylase Activity in the Frontal Cortex and Hippocampus. Soc. Neurosci. Abstr. 13, 464.6 (1987).

The tryptophan hydroxylase (TPH) activity of rat frontal cortex and hippocampus was found to decrease seven days following an acute large dosage of MDMA. The latter area was spared enzyme loss with adrenalectomy.

Johnson, M., Hanson, G.R. and Gibb, J.W. Effect of MK-801 on the Decrease in Tryptophan Hydroxylase Induced by Methamphetamine and its Methylenedioxy Analog. Europ. J. Pharmacol. 165 315-318 (1989).

Repeated injections of methamphetamine or MDMA in rats reduced neostriatal TPH activity. If MK-801 is administered concurrently the methamphetamine depletion of enzyme is attenuated, but the MDMA induced depletion is not. There may be some involvement of NMDA receptors.

Johnson, M., Mitros, K., Stone, D.M., Zobrist, R., Hanson, G.R. and Gibb, J.W. Effect of Flunarizine and Nimodipine on the Decrease in Tryptophan Hydroxylase Activity Induced by Methamphetamine and 3,4-Methylenedioxymethamphetamine. J. Pharm. Exptl. Therap. 261 586-591 (1992).

The effects of calcium channel blockers on the decrease of central tryptophan hydroxylase activity and serotonin concentration induced by repeated large doses of methamphetamine and MDMA were evaluated. The results suggest that calcium influx may participate in these responses.

Kumagai, Y., Lin, L.Y., Schmitz, D.A. and Cho, A.K. Hydroxyl Radical Mediated Demethylation of (Methylenedioxy)phenyl Compounds. Chem. Res. Toxicol. 4 330-334 (1991).

The oxidative demethylation of methylenedioxybenzene, MDA and MDMA was achieved with two hydroxy iron-containing radical systems, one with ascorbate and one with xanthine oxidase. Hydrogen peroxide alone was not effective in producing the metabolite catechols.

Kumagai, Y., Wickham, K.A., Schmitz, D.A. and Cho, A.K. Metabolism of Methylenedioxyphenyl Compounds by Rabbit Liver Preparations. Biochem. Pharmacol. 42 1061-1067 (1991).

The demethylation of methylenedioxybenzene, MDA and MDMA is a major metabolic pathway, and is achieved in the microsomal fraction by the action of P-450. Studies involving inducers and suppressors indicate that several isozymes are involved in the formation of the product catechols.

Letter, A.A., Merchant, K., Gibb, J.W. and Hanson, G.R. Roles of D2 and 5-HT<sub>2</sub> Receptors in Mediating the Effects of Methamphetamine, 3,4-Methylenedioxymethamphetamine, and 3,4-Methylenedioxyamphetamine on Striato-Nigral Neurotensin Systems. Soc. Neurosciences Abstrts. 12 1005 (# 277.7) 1986.

The chronic treatment of rats with methamphetamine, MDA or MDMA leads to a 2-3x increase of the neurotensin-like immunoreactivity in the striato-nigral areas of the brain. Efforts to assign neurotransmitter roles led to the simultaneous administration of serotonin and dopamine antagonists. These interrelationships are discussed.

Merchant, K., Letter, A.A., Stone, D.M., Gibb, J.W. and Hanson, G.R. Responses of Brain Neurotensin-like Immunoreactivity to 3,4-Methylene-dioxymethamphetamine (MDMA) and 3,4-Methylenedioxyamphetamine (MDA). Fed. Proc. 45 1060 (# 5268) (1986).

The administration of MDA and MDMA profoundly alters the levels of neurotensin-like immunoreactivity (NtLI) concentrations in various portions of the brain of the rat. Increases of up to a factor of 3x are observed in some regions of the brain.

Nash, J.F. and Meltzer, H.Y. Neuroendocrinological Effects of MDMA in the Rat. The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA. Kluwer, New York. (1990) Ed: S.J. Peroutka.

MDMA has been observed to increase plasma ACTH and corticosterone concentrations in a dose-dependent manner. A series of pharmacological challenges suggests that serotonin release may be a responsible factor.

Poland, R.E. Diminished Corticotropin and Enhanced Prolactin Responses to 8-Hydroxy-2-(di-n-propylamino)tetralin in Methylenedioxymethamphetamine Pretreated Rats. Neuropharmacology 29 1099-1101 (1990).

Pretreatment of rats with a single, modest dose of MDMA followed by a challenge with the serotonin agonist 8-OH DPAT led to a decrease corticotropin and an enhanced prolactin response. This suggests that MDMA produces abnormal serotonin receptor-coupled neuroendocrine responses.

Schmidt, C.J. and Taylor, V.L. Acute Effects of Methylenedioxymethamphetamine (MDMA) on 5-HT Synthesis in the Rat Brain. Pharmacologist 29 ABS-224 (1987). See also: Biochemical Pharmacology 36 4095-4102 (1987).

Acute exposure of MDMA dropped the tryptophane hydroxylase activity of rats, and this persisted for several days. Subsequent administration of Fluoxetine recovered this activity, but reserpine or alpha-methyl-tyrosine did not.

Stone, D.M., Hanson, G.R. and Gibb, J.W. GABA-Transaminase Inhibitor Protects Against Methylenedioxy-methamphetamine (MDMA)-induced Neurotoxicity. Soc. Neurosci. Abstr. Vol. 13, Part 3 (1987). # 251.3.

The neurotoxicity of MDMA (in the rat) was protected against by GABA-transaminase inhibitors.

Stone, D.M., Johnson, M., Hanson, G.R. and Gibb, J.W. A Comparison of the Neurotoxic Potential of Methylenedioxyamphetamine (MDA) and its N-methylated and N-ethylated Derivatives. Eur. J. Pharmacol. 134 245-248 (1987).

Multiple doses of MDA and MDMA decreases the level of brain tryptophan hydroxylase (TPH). The N-ethyl homologue was without effect. It is argued that although the studies here were well above human exposures, the cumulative effects of repeated exposures, the differences between rat and human metabolism, and increased human sensitivity to this drug, could present a serious threat to human abusers of this drug.

Stone, D.M., Johnson, M., Hanson, G.R. and Gibb, J.W. Acute Inactivation of Tryptophan Hydroxylase by Amphetamine Analogs Involves the Oxidation of Sulfhydryl Sites. Europ. J. Pharmacol. 172 93-97 (1989).

MDMA, Fenfluramine and methamphetamine, separately, reduced the tryptophan hydroxylase activity in rat brain. The enzyme activity could be restored, in the cases of the latter two drugs, by treatment that suggested that some reversible oxidation of sulfhydryl groups was involved. With MDMA, the changes were irreversible, and serotonergic toxicity is suggested.

Stone, D.M., Stahl, D.C., Hanson, G.R. and Gibb, J.W. Effects of 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) on Tyrosine Hydroxylase and Tryptophane Hydroxylase Activity in the Rat Brain. Fed. Proc. 45 1060 (# 5267) April 13-18, 1986.

The effects of rats treated chronically with either MDA or MDMA on the enzymes involved with neurotransmitter synthesis is reported. The levels of tryptophane hydroxylase (TPH, involved with serotonin synthesis) were markedly reduced, differently in different areas of the brain. The tyrosine hydroxylase (TH, involved with dopamine synthesis) remains unchanged. This is in contrast to the documented reduction of TH that follows high dosages of methamphetamine.

Wilkerson, G. and London, E.D. Effects of Methylenedioxymethamphetamine on Local Cerebral Glucose Utilization in the Rat. Neuropharmacology 28 1129-1138 (1989).

MDMA was found to influence glucose utilization at some 60 different areas in the rat brain, as determined by the employment of radioactive 2-deoxyglucose. A thorough tally has been made of these areas, and the changes that follow four different dose levels of exposure.

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