Anderson, Paul Michael; Hutchinson, Mark Rowland; Irvine, Rod; Salem, Abdallah Mohamed

Attenuating glial activation with minocycline reduces the hyperthermic response to 3, 4-methylenedioxymethamphetamine (MDMA) in the rat, The Open Addiction Journal, 2011; 4(Sp Iss):4-5

© Anderson et al.; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.

PERMISSIONS

http://benthamscience.com/open/toaddj/MSandI.htm

- Articles are licensed under the terms of the Creative Commons Attribution non-commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, providing that the work is properly cited.

21st December 2012

http://hdl.handle.net/2440/68792
Attenuating Glial Activation with Minocycline Reduces the Hyperthermic Response to 3, 4-Methylenedioxymethamphetamine (MDMA) In the Rat

P. Anderson*, M.R. Hutchinson, R.J. Irvine and A. Salem

Discipline of Pharmacology, School of Medical Sciences, University of Adelaide, SA 5005, Australia

Keywords: 3,4-Methylenedioxymethamphetamine, “ecstasy”, hyperthermia, microglia, minocycline.

INTRODUCTION

Hyperthermia is a key clinical outcome from recreational use of MDMA and is the leading cause of MDMA related hospital admissions as well as being linked to enhanced neurotoxicity [1, 2]. Animal models of ischemia which also display hyperthermia have shown an inflammatory process mediated by microglia and the release of the pro-inflammatory cytokine interleukin 1-β (IL-1β) play a role in hyperthermic reactions [3]. Previous studies showed that microglia is prominently activated and IL-1β levels increased following MDMA administration [4], lending support to the hypothesis microglia play a role in MDMA induced hyperthermia. Minocycline is a tetracycline antibiotic with powerful anti-inflammatory properties, thought to be a result of its ability to attenuate glial activation [5]. This study examined whether preventing microglial activation through the administration of minocycline could limit or prevent the hyperthermia induced by MDMA.

METHODS

Male Sprague-Dawley rats were treated daily with 50 mg/kg i.p. of minocycline (or vehicle control) for two or three days (Fig. 1). 30 min following the final dose they were administered 10 mg/kg i.p. of MDMA with core body temperature and behavioral measurements taken every half hour (from 2 hr prior to 4 hr post MDMA treatment). Experiments were conducted at a normal ambient temperature of 22°C. The animals were then anaesthetised with Chloral Hydrate (400mg/kg i.p.), core blood was taken and the brain quickly removed and stored at -70°C. Blood and brain levels of MDMA and its major metabolite 3,4-methylenedioxyamphetamine (MDA) were measured using HPLC-ED and levels of IL-1β in the cortex and striatum were analysed using an ELISA assay. Temperature measurements and IL-1β levels were analysed using a two-way ANOVA with Bonferroni’s post-hoc test. Plasma and brain levels of MDMA and MDA were analysed using one-way ANOVA with Tuckey’s post-test. Behavioural data was compared using the Kruskal-Wallis test. P < 0.05 was taken as significant for all analyses.

RESULTS

MDMA treated animals showed significant increases in core temperature compared with rats treated with saline (p = 0.0001, n=6). Minocycline alone had no significant effect on core temperature. Animals administered MDMA and minocycline had a significantly reduced rise in temperature compared to MDMA treated animals (p<0.01, n=6). Behavioural measures showed no significant differences between animals receiving minocycline and those not, but did between MDMA and saline treated animals (n=6, P<0.0001). Minocycline had no significant effect on either blood (p =0.940, n=8) or brain (p =0.9296, n=8) concentrations of MDMA and MDA. An interleukin 1-beta assay was performed on cortex, this showed no significant differences between any of the treatment groups, (p = 0.5235, n=4).

DISCUSSION

The major findings of this study are that the pre-treatment administration of minocycline significantly attenuates the hyperthermia induced by MDMA administration in rats. Minocycline also had no significant impact on MDMA-induced behavioural stimulation, supporting the hypothesis that an inflammatory response
Attenuating Glial Activation with Minocycline

plays a role in MDMA induced hyperthermia; independent

of serotonin and dopamine mediated behavioural stimu-

lation. Further evidence in support of this hypothesis is the

finding of similar brain and plasma concentrations of

MDMA and MDA with and without the co-administration of

minocycline. Both compounds were detected at similar

levels regardless of minocycline treatment indicating that

minocycline’s action is not due to changes in MDMA

pharmacokinetics.

CONCLUSION

The results of this study indicate that the mechanisms

underlying MDMA induced hyperthermia may include an

inflammatory response mediated by microglia. These results

also indicate that immune status may be a factor in the

apparently idiosyncratic effects of MDMA on hyperthermia

in some individuals and as such preventing or inhibiting glial

activation may be a clinically relevant method of treating

MDMA toxicity.

REFERENCES

[1] Malberg JE, Seiden LS. Small changes in ambient temperature

cause large changes in 3,4- methylenedioxymethamphetamine

(MDMA)-induced serotonin neurotoxicity and core body tempe-


[2] Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The

pharmacology and clinical pharmacology of 3, 4-methylenedioxy-

methamphetamine (MDMA, "ecstasy"). Pharmacol Rev 2003;


A. Rapidly activated microglial cells in the preoptic area may play

a role in the generation of hyperthermia following occlusion of the

middle cerebral artery in the rat. Exp Brain Res 2003; 153(1): 84-

91.

[4] Orio L, O'Shea E, Sanchez V, et al. 3, 4-Methylenedioxy-metham-

phetamine increases interleukin-1β levels and activates microglia

in rat brain: studies on the relationship with acute hyperthermia and


[5] Stirling DP, Koochesfahani KM, Steeves JD, Tetzlaff W. Minocy-

cline as a neuroprotective agent. Neuroscientist 2005; 11(4): 308-

22.