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Attenuating Glial Activation with Minocycline Reduces the Hyperthermic Response to 3, 4-Methylenedioxymethamphetamine (MDMA) In the Rat

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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-1 β) play a role in hyperthermic reactions [3]. Previous studies showed that microglia is prominently activated and IL-1 β 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-1 β in the cortex and striatum were analysed using an ELISA assay. Temperature measurements and IL-1 β 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 Tukey'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, ($p = 0.5235$, $n=4$).

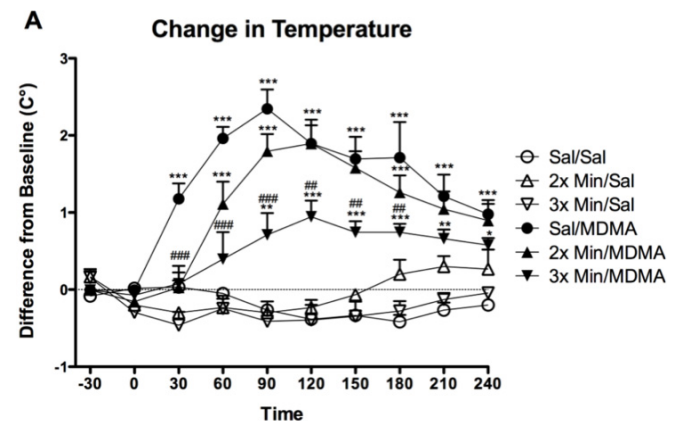


Fig. (1). Effect of MDMA co-administered with minocycline (2 day treatment [2x Min] or 3 day treatment [3x Min]) on core body temperature, represented as the change from baseline temperature (mean of temperature recorded at -60, -30 and 0 mins). Saline (Sal) or Min was administered at -30 min; Sal or MDMA (10 mg/kg, i.p.) was administered at 0 min. Data are given as mean + SEM ($n = 6$).

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

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plays a role in MDMA induced hyperthermia; independent of serotonin and dopamine mediated behavioural stimulation. 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.

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