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# The effect of 3,4-methylenedioxymethamphetamine ('Ecstasy') on serotonergic regulation of the mammalian circadian clock mechanism in rats: the role of dopamine and hyperthermia

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**Abstract**

The recreational drug 3,4-methylenedioxymethamphetamine (MDMA) is known to be a neurotoxin for serotonergic axons ascending from the raphe nucleus including those which terminate on neurons of the suprachiasmatic nuclei (SCN) of the hypothalamus, the putative mammalian circadian clock. Since dopamine release has been implicated in the serotonergic neurotoxicity, we examined the effects of the dopamine synthesis inhibitor alpha-methyl-p-tyrosine (AMPT) and the D2 receptor antagonist haloperidol (HAL) on the long-term effect of MDMA on serotonergic regulation of the SCN neuronal firing rhythm. Co-administration of AMPT or HAL with MDMA eliminated the acute hyperthermic response but had no effect on the MDMA-induced phase shift in the firing rhythm of SCN neurons to the selective 5-HT1A receptor agonist, 8-hydroxy-2-(dipropylamino)-tetralin. It is concluded that neither dopamine metabolism nor hyperthermia account for the altered serotonergic function in the SCN produced by MDMA. Toxic free radical production following MDMA metabolism may be responsible.



*Keywords:* 3,4-Methylenedioxymethamphetamine; Neurotoxicity; Dopamine; Suprachiasmatic nuclei; Circadian rhythm

In rats and primates 3,4-methylenedioxymethamphetamine (MDMA) is a serotonin neurotoxin. Repeated moderate doses of MDMA produce selective loss of fine-diameter 5-HT-containing neurons throughout the forebrain in both rats and monkeys [14]. In addition, tissue levels of 5-HT and densities of 5-HT reuptake sites and 5-HT immunoreactive fibres in the forebrain are depleted for up to many weeks following repeated MDMA dosing [21]. Dosing protocols are important in determining MDMA effects on the brain and it is clear that multiple high dosing, as used in the present study, is often required to produce reliable evidence of neurotoxicity, although in one case a single dose of 10 mg/kg was sufficient [6]. While some recovery and reinnervation may occur even after such dosing the rat data suggest that both MDMA and other selective 5-HT neurotoxins such as 5,7-Dihydroxytryptamine cause damage which is still apparent after 6 months [1,3]. In addition, previous suprachiasmatic nuclei (SCN) slice preparation data show that despite some possible recovery there is still a lasting effect of the MDMA regimen on the SCN neurons at 20 weeks after administration [2].

Recently, MDMA has been shown to alter the response of the circadian clock to photic and non-photic stimuli in vivo [7,19] and to attenuate the normal phase advance in the firing rhythm of single neurons in the SCN to a serotonin agonist in a rat hypothalamic tissue slice preparation in vitro [2]. Since in humans, rhythm disorders are linked to changes in sleep patterns and mood and mental performance changes [9], this effect could explain some of the reported negative changes commonly associated with recreational MDMA, although since most MDMA users also use other drugs such as cannabis, such negative effects must be treated cautiously. The effect of MDMA on the circadian clock probably reflects damage to the axon terminals of serotonergic fibres originating in the raphe nucleus. Since there is evidence that MDMA primarily targets the fine serotonin axon fibres which leave the dorsal raphe nucleus (DRN) and affect the SCN via neurons of the intergeniculate nucleus (IGN) it is probable that the effect of MDMA on the clock acts via this route rather than by affecting the serotonergic beaded axons which pass directly from the median raphe nucleus (MRN) to the SCN [18]. In any case it is clear that the serotonergic raphe fibres are involved

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because lesions of the raphe nucleus, or chemical depletion of brain serotonin alters circadian function [16], and in addition, serotonin agonists such as quipazine and 8-hydroxy-2-(dipropylamino)-tetralin (8-OH-DPAT) can reset the phase of the circadian clock when directly administered to the SCN tissue slice preparation in vitro [2]. The mechanism responsible for the MDMA-induced damage to the raphe fibres is not understood. In particular, it is not known whether the mechanism underlying the change to the circadian clock is the same as that which is responsible for the general serotonergic neurotoxicity in forebrain, striatum and hippocampus which has been widely reported.

One account of MDMA's neurotoxic effect implicates both dopamine release and the generation of oxidative free radicals [26]. According to this account MDMA neurotoxicity involves an acute release of 5-HT and dopamine, the activation by 5-HT of post-synaptic 5-HT2A/2C receptors on GABA interneurons resulting in reduced GABAergic transmission and increased dopamine release, the transport of the excessive dopamine into the depleted 5-HT terminal, followed by its deamination and the production of toxic free radicals. Such an account has been supported by reports of increased dopamine release following MDMA administration [23], reduced serotonergic neurotoxicity and hyperthermia following co-administration of MDMA and drugs which reduce the availability and/or effectiveness of dopamine such as alpha-amino-p-tyrosine (AMPT), a dopamine synthesis inhibitor, and haloperidol (HAL), a D2 receptor antagonist [11,13,22]. In addition, decreased neurotoxicity following administration of antioxidants such as cysteine and ascorbic acid has been reported [25]. In contrast, dopamine involvement is questioned by studies which found no evidence of a causal role of dopamine in serotonergic neurotoxicity when body temperature changes were controlled for [28], and were unable to demonstrate a potentiation of MDMA-induced toxicity in response to administration of the dopamine precursor, L-DOPA [5]. Some researchers have proposed that toxic metabolites of MDMA produced after uptake of MDMA into 5-HT neurons may be responsible for the neurotoxicity. It is known that MDMA is metabolized to catechol and quinone metabolites [12] and it is possible that these substances may be further metabolized to produce free radical and oxidative stress after absorption into neuron terminals via a mechanism involving the 5-HT transporter [6]. Indirect support for such an account comes from the findings that the 5-HT uptake inhibitor, fluoxetine, prevents the increase in free radical formation that normally follows MDMA and also prevents the neurodegeneration of 5-HT nerve endings [20]. The situation is complicated by the fact that MDMA-induced hyperthermia itself is implicated as a possible causal mechanism of neurotoxicity and evidence showing that some dopamine antagonists may exert their neurotoxic protection by blocking the hyperthermic response to MDMA. For example, procedures which act to maintain the hyperthermia in the presence of dopamine antagonists (such as heating the animal in a thermal blanket or raising ambient temperature) can prevent the protective action [13,28]. On the other hand, it is unlikely that hyperthermia alone is a sufficient explanation for MDMA neurotoxicity since some agents such as fluoxetine and fluvoxamine have been found to be neuroprotective while having no effect on the acute hyperthermic response of MDMA [20]. Thus, while the role of oxidative free radicals in MDMA's serotonergic neurotoxicity is fairly well accepted it is not clear to what extent dopamine and/or acute hyperthermia is directly involved.

The aim of the present study was to examine whether dopamine and/or hyperthermia is involved in the long-term serotonergic effect of MDMA on the circadian clock mechanism. To the extent that dopaminergic mechanisms are involved, co-administration of a neurotoxic dose of MDMA and either the dopamine synthesis inhibitor (AMPT) or the D2 antagonist (HAL) should attenuate the altered in vitro SCN neuronal response to the serotonin agonist 8-OH-DPAT which follows MDMA treatment. Biotelemetry was used to monitor the acute body temperature response to MDMA in order to confirm the effectiveness of HAL and AMPT in blocking the MDMA-induced hyperthermia as has been previously reported [11,13].

For the experiment, Male Wistar rats (Charles River, UK) were used. They were housed under a 12/12 h light/dark cycle (lights on at 07:00 h) and given food and water ad libitum. Rats were assigned to one of the following five groups which received drug treatments s.c. once/day for three successive days ($N = 7$ in each case): MDMA-ONLY (MDMA 20 mg/kg body weight s.c.); MDMA-AMPT (AMPT 75 mg/kg s.c. followed after 60 min by MDMA 20 mg/kg); MDMA-HAL (HAL 2 mg/kg followed after 15 min by MDMA 20 mg/kg); AMPT-ONLY (AMPT 75 mg/kg); HAL-ONLY (HAL 2 mg/kg). MDMA was administered as the hydrochloride salt dissolve in buffered saline. Two other groups of rats were used only in the in vitro tissue slice phase of the experiment (NO TREATMENT and DPAT ONLY). As in previous studies the mean peak in the firing rate of slices taken from the NO TREATMENT group was used as a baseline for calculation of the phase shifts in the firing rhythm of the treated groups [2]. Drugs were administered at 11:00 h, 4 h into the light section of the light/dark cycle and during the low phase of the diurnal temperature and activity cycle. Rats were sacrificed for in vitro recording 20–30 weeks after drug treatment. The experiment was performed under Home Office Project Licence No. 60/2849.

Body temperature was monitored continuously at 10 min intervals for a period commencing 48 h prior to the first drug treatment and finishing 24 h after the last drug treatment by means of a computer controlled remote biotelemetry system (Data Sciences Inc., Lab Pro System 4). The system has been described fully previously [8] but briefly, wax-coated transmitters (model TA10TA-F40) are implanted under anaesthesia (halothane) in the rats' abdominal cavity and

emit radio-frequency pulses (range 300–600 Hz) whose frequency varies linearly with temperature in the physiological range. Receivers (model RA1010) located beneath each cage transmit the frequency information to a computer which records and analyzes the data. The acute effect of the drug treatments was assessed by subtracting from all of the temperature scores sampled during the 6 h post-treatment period on each drug day the scores recorded during the equivalent time period on the day preceding the first drug day. The maximal difference score was taken as the peak temperature score. Summing the difference scores over the 6 h period produces an 'area-under-the-curve' (AUC) measure which takes into account both the magnitude and the duration of the temperature change. Analysis of variance (ANOVA) and post-hoc Tukey HSD tests were used to examine the significance of the treatment effects on both peak and AUC measures.

For tissue preparation, rats were administered an overdose of halothane anaesthesia and decapitated during the phases when this does not induce phase shifts, between 2 and 5 h after lights on time (i.e. Zeitgeber Time (ZT) 2–5). Hypothalamic slices (500 μm) containing the SCN were placed in a gas–fluid interface slice chamber (Medical Systems BSC with Haas top), continuously bathed (1 ml/min) in artificial cerebro-spinal fluid (ACSF) containing 125.2 mM NaCl, 3.8 mM KCl, 1.2 mM $KH_2PO_4$, 1.8 mM $CaCl_2$, 1 mM $MgSO_4$, 24.8 nM $NaHCO_3$, and 10 mM glucose. ACSF (pH 7.4) was supplemented with an antibiotic (gentamicin, 0.05 g/l) and maintained at 34.5 °C. Warm, humidified 95% oxygen/5% carbon dioxide was continuously provided.

Extracellular single unit activity of SCN cells was detected with glass micropipette electrodes filled with 2 M NaCl, advanced through the slice using a hydraulic microdrive. The signal was fed into an amplifier for further amplification and filtering, and was continuously monitored by an oscilloscope and audio monitor. Firing rate and interspike interval data were analyzed using data acquisition software and a customized program for calculation of descriptive statistics. The person recording cells was blind to all treatments. Shifts in the peak of the firing rate were calculated with respect to peaks in the untreated control slices (group NO TREATMENT) which had ACSF administered at ZT 8. Treatments to the hypothalamic slice were applied as a 200 nl microdrop to the SCN area at least 1 h after slice preparation, on the same day as slice preparation. Recordings were performed for at least 12 h, during ZT 0–12 of the second 24 h in vitro (i.e. ZT 24–36). Treatments were warmed to 34.5 °C. The concentration of 8-OH-DPAT (10 μM in ACSF) was similar to those used in previous studies [2,16]. 8-OH-DPAT was purchased from Sigma (Poole, Dorset, UK) and applied in a 200 nl volume. 8-OH-DPAT (or ACSF in groups NO TREATMENT, HAL ONLY and AMPT ONLY) was manually placed onto the area of the SCN in the brain slice at ZT 8 using a Hamilton 1 μl syringe (microdrop application).

Problems with probes and/or missed recordings meant that the *N*s for the five drug treatment groups in the in vivo temperature monitoring stage were 6, 5, 6, 7 and 7. Administration of MDMA on each of three successive days produced a pronounced hyperthermia (see Fig. 1). Co-administration of AMPT or HAL with MDMA (groups AMPT/MDMA and HAL/MDMA) reversed the direction of the thermic response producing a profound hypothermia. Administration of the dopaminergic agents alone (AMPT ONLY and HAL ONLY) had no significant effect on body temperature. The peak temperature change in the 6 h post-drug period for each subject (point of maximal difference from the pre-drug day baseline) was analyzed in a two-way ANOVA with Group and Days as factors. There was a highly significant effect of Group ($F(4, 26) = 35.53$, $P < 0.00001$) and a non-significant Days effect ($F(2, 52) = 1.24$, $P = 0.3$). The Group × Days interaction was also just significant ($F(8, 52) = 2.33$, $P < 0.05$), presumably due to the trend over the three treatment days towards decreasing hyperthermia in group MDMA ONLY and decreasing hypothermia in groups AMPT/MDMA and HAL/MDMA. Post-hoc Tukey HSD tests showed that group MDMA ONLY differed significantly from groups AMPT/MDMA and HAL/MDMA on all treatment days and from groups AMPT ONLY and HAL ONLY on treatment days 1 and 2 ($P < 0.05$ in each case).

Similar results were found for the area-under-the-hyperthermia-curve (AUC) data. ANOVA revealed a significant main effect of Treatment ($F(2, 26) = 47.74$, $P < 0.0001$) and a significant Treatment × Days interaction ($F(8, 52) = 3.78$, $P < 0.005$). Post-hoc Tukey tests showed that the MDMA ONLY group differed from groups AMPT/MDMA and HAL/MDMA on each treatment day ($P < 0.01$ in each case) and differed from groups AMPT ONLY and HAL ONLY on the first treatment day only due

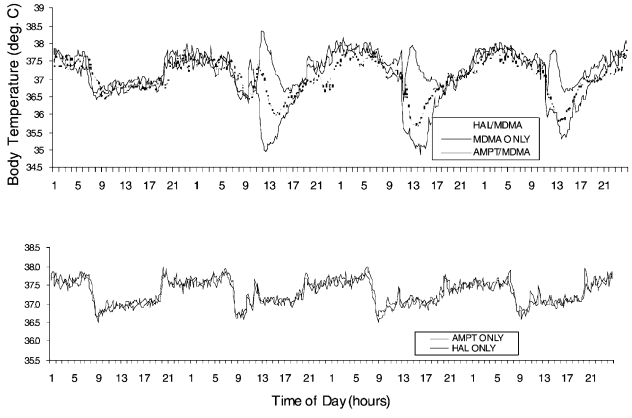


Fig. 1. Body temperature (smoothed using a 60 min running average) plotted against time of day over the pre-treatment day and three treatment days. MDMA injections were administered at 11:00 h each day during the low phase of the circadian temperature rhythm. The onset of the light period was 07:00 h. For clarity, groups AMPT ONLY and HAL ONLY are shown separately.

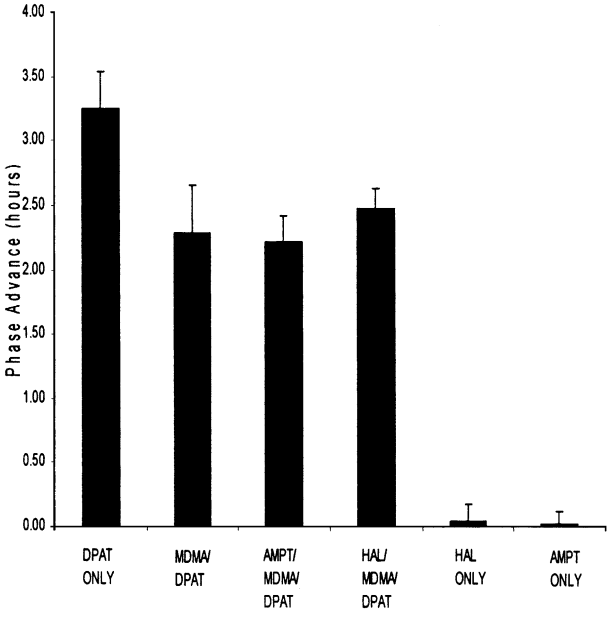


Fig. 2. Phase advance (hours) in SCN neuron peak firing rates in slices taken from the different treatment groups. Values are calculated with respect to control slices from the NO TREATMENT group.

to the habituated thermic response to MDMA on the second and third treatments.

In the analysis of the in vitro tissue slice data, the shift in phase of SCN neurons (relative to the NO DRUG control slices) for all groups to a test dose of the 5-HT agonist 8-OH-DPAT is shown in Fig. 2.

Pre-treatment with a neurotoxic regimen of MDMA (MDMA/DPAT) attenuates the usual shift in firing rhythm produced by 8-OH-DPAT alone (DPAT ONLY). Importantly, the co-administration of dopamine antagonists AMPT and HAL with MDMA (groups AMPT/MDMA/DPAT and HAL/MDMA/DPAT) did not affect MDMA's attenuation of DPAT's effect. Prior administration of HAL or AMPT alone had no effect on the SCN firing rhythm under administration of ACSF (AMPT ONLY and HAL ONLY). ANOVA revealed a significant Group effect ($F(5, 24) = 147.2$, $P < 0.0001$). Tukey tests showed that groups MDMA/DPAT, HAL/MDMA/DPAT and AMPT/MDMA/DPAT did not differ from each other, but that each differed significantly from group DPAT ONLY and from groups HAL ONLY and AMPT ONLY ($P < 0.001$ in each case).

The aim of this study was to determine whether dopamine release, which has been implicated in MDMA's neurotoxic effect on serotonin pathways in the brain, is also involved in the altered responsiveness of the circadian clock mechanism of the SCN to a neurotoxic dose of MDMA. Our findings suggest that dopamine release is not a factor in the altered SCN response. The ability of a neurotoxic dose of MDMA to attenuate the phase shift in firing of SCN neurons produced by 8-OH-DPAT, a 5-HT1A agonist, was not affected by the co-administration of either AMPT or HAL. AMPT is a dopamine synthesis inhibitor and HAL is a D2 receptor antagonist. Both agents have been shown to reduce dopamine release in response to MDMA, and to attenuate the neurotoxic and behavioural effects of MDMA [11,13]. Since, in the current experiment, the doses of AMPT and HAL used were sufficient to abolish the acute hyperthermia induced by MDMA, our findings also argue against a causal role for hyperthermia-induced neurotoxicity in the altered SCN response. As such, our results may be taken as indirect evidence for an alternative mechanism for MDMA neurotoxicity in the SCN. Since evidence for the role of neurotoxic hydroxyl radicals is strong [6,4,24] it is possible that MDMA itself, rather than dopamine, may be a source of such radicals in the SCN. The metabolism of MDMA generates catechols and quinones that can produce free radicals [5]. Furthermore, such radicals may act upon the 5-HT released by MDMA to generate other neurotoxic agents which operate via the 5-HT transporter [27]. A similar mechanism may account for MDMA-induced serotonergic neurotoxicity in other areas of the brain which lack significant dopaminergic innervation, such as the somatosensory cortex [10].

The influences of serotonin on the circadian clock mechanisms are complex and may be multiple. Two anatomical components of the circadian regulatory mechanism, the SCN and the intergeniculate leaflet (IGL), receive serotonergic input from the midbrain raphe nucleus, with cells of the SCN receiving input from the MRN and cells of the IGL receiving input from the DRN. However, recent immunohistochemical evidence is less supportive of the general view that specific axon types and varicosities are related specifically to raphe nucleus of origin showing that in hamsters the dense serotonergic innervation of the SCN from the MRN is exclusively fusiform and of small diameter [17]. Species differences may also be important. In hamsters, selective depletion of 5-HT within or selective destruction of these raphe regions implicates the MRN-SCN pathway as crucial in circadian regulation [15], while in rats, evidence suggests a selective targeting of MDMA for the fine fibres leaving the dorsal raphe [11]. While it is also possible that MDMA exerts its effects on the circadian clock in some non-specific way which does not involve serotonergic neurotoxicity at all, this is unlikely since the shift in SCN firing rhythm to other agents involved in circadian regulation such as neuropeptide-Y (NPY) and pituitary adenylate cyclase-activating peptide (PACAP) is unaffected by pre-treatment with MDMA [2]. Future studies employing specific 5-HT receptor agonists/antagonists and free radical scavengers may be crucial in unravelling the effects of MDMA in the SCN.

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