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ORIGINAL INVESTIGATION

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Decreased pain tolerance and mood in recreational users of MDMA

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA) is known to affect brain serotonin (5-HT) neurons in experimental animals. However, its effects on humans are more difficult to infer. Serotonin is implicated in the body's ability to modulate the effects of pain and to regulate mood. *Objective:* The aim of this research is to test nociceptive responses and mood in MDMA users as an index of central 5-HT function. *Method:* Measurements of pain tolerance were obtained using the cold-pressor test for 15 polydrug users who regularly use MDMA, 3–4 days after the most recent usage, and ten matched polydrug users who do not use MDMA. A rating on mood was obtained for each participant using the Nowlis Mood Adjective checklist. *Results:* Measurements of pain tolerance and mood were significantly lower in the MDMA group. A positive correlation between mood and pain tolerance was found in the MDMA group, whereas no correlation was found between these variables in the non-MDMA group *Conclusion:* This study found an association between pain tolerance and MDMA usage and confirmed the association between MDMA and depressed mood. The current results suggest that MDMA, at least in the short term, may cause serotonin-mediated alterations in pain sensitivity.

Keywords MDMA · Serotonin · Nociception · Pain tolerance · Mood

Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a synthetic amphetamine derivative, with mixed stimulant and hallucinogenic properties (Solowij 1993). Most commonly known as ecstasy, it inhibits the re-uptake and promotes the release of serotonin (5HT) in the brain (Green et al. 1995). MDMA has been shown to cause serotonergic neuronal toxicity in animal studies (Ricaurte et al. 1988, 1989, 1992); however, in humans, such direct causation is more difficult to infer.

Affective and psychotic disturbances are increasingly being recognised in association with MDMA use and the effects are widespread at the behavioural as well as the neurochemical level (for animal studies, see Lin et al. 1999; Morley and McGregor 2000; Daws et al. 2000; Maldonado and Navarro 2000, 2001; for human studies, see Schifano et al. 1998; Croft et al. 2001; Gerra et al. 2001; Parrot 2001). As many experiments undertaken with animals are impossible to replicate in humans, indirect approaches are a valuable way to assess the effects of MDMA on the serotonergic system in humans. One approach that has been largely ignored in humans is the effect of MDMA on nociception: serotonin is implicated in the modulation of pain therefore abuse of any substance which alters its levels should manifest itself in altered pain sensitivity.

Studies of MDMA in animals do suggest a direct serotonergic-mediated effect on nociception. Experimental animal models designed to test acute antinociceptive, or analgesic, effects have provided evidence suggestive of a role for MDMA in the control of pain. Crisp et al. (1989) examined the antinociceptive effects of MDMA in rats and found a dose-dependent reduction in pain sensitivity using measurements of hot-plate latency. The analgesic effects of MDMA on the hot-plate test were reversed by a serotonergic antagonist, thus implying that the antinociceptive effects of MDMA are serotonergically mediated. More recently Morley-Fletcher et al. (2002) found that acute treatment with MDMA induced analgesia and suggested a role for 5-HT in this process. Nociception was measured 1 h after administration of MDMA.

All of these studies, however, tested noception after acute administration of MDMA when the largest increases in levels of 5-HT would have been expected. Nishi-

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sawa et al. (1999) found the rate of serotonin synthesis to be 6 times greater than the baseline 1 h after injection of MDMA in dogs. The focus of this study is to test nociception in the days after MDMA use, targeting the period of serotonin depletion.

Extensive investigations over the past quarter century have greatly expanded our understanding of the nervous system pathways that process and modulate pain. In anaesthetised animals, Zimmerman (1984) found that the firing of dorsal horn neurons in response to noxious skin heating could be inhibited by stimulation in the periaqueductal gray (PAG) area of midbrain. The dorsolateral funiculus is the descending serotonin inhibitory system that arises in the nucleus raphe magnus of the medulla and the PAG area of the midbrain and exerts its effect on neurons in the dorsal horn. Inhibition can also be achieved by electrical stimulation in other regions of the brain, such as the raphe nuclei, where cell bodies of 5-HT pathways arise (Sandkuhler and Gebhart 1984). Animal studies have shown that when serotonin is added directly to the central nervous system, it accumulates in the periventricular areas and enhances the effectiveness of analgesia produced by electrical stimulation, and decreased pain perception (Gershon 1986). Furthermore, studies have shown that blocking presynaptic reuptake of serotonin, increases the level of serotonin in the presynaptic cleft, and consequently reduces the sensitivity to pain (Gershon 1986). This is the principle underlying treatment of pain with antidepressants (Ads) especially SSRIs (selective serotonin reuptake inhibitors). The evidence consistently indicates that ADs may have an antinociceptive effect on human pain; for a review, see Fishbain (2000).

Pain perception is therefore a complex mechanism involving modulation from both the peripheral and central nervous system. Descending serotonergic pathways are known to attenuate pain signals reaching the brain (Willis and Westlund 1997). MDMA causes a short-term increase in synaptic levels of serotonin with a shortfall 3–4 days post-ingestion. This current study was designed to investigate if pain tolerance is decreased in MDMA users, 3–4 days after the most recent usage. Previous research on humans by McCann et al. (1994) found no significant difference in pain measures between MDMA users and a non-drug taking control group however their participants had not taken MDMA for at least 18 weeks. Testing in this study will target the "midweek" period of neurochemical depletion when a shortfall of serotonin is predicted. This is identified as the time when the proposed effect on noiception should be most pronounced.

Males were chosen for testing in view of the following considerations. Firstly, there are differences between males and females in levels of serotonin within the spinal column (Berkley 1997). Serotonin concentration in the spinal cord of lab animals is much higher in males than females. This suggests, that the serotonergic influences on the processing of information (including pain signals) would be greater in males than females (Berkley 1997). Also, there is a large shift in the way the central nervous system chemicals are produced (including serotonin) with response to the different stages of the female cycle, and animal and human research has shown that pain sensitivity changes during the menstrual cycle (Hellström and Lundberg2000).

Recreational MDMA users typically describe a range of positive moods while on MDMA (Parrott and Stuart 1997); however, negative moods have been reported during the period of neurochemical depletion in the days afterwards (Parrott and Stuart 1997, Davison and Parrott 1997). Research by Weisenberg et al, (1998) suggests that mood may induce physiological changes that affect the sensory components of pain. This study will therefore also explore associations between participant's mood on the same day as testing pain tolerance.

Methods and materials

Participants

After approval by the University ethics committee and after written informed consent, 25 male participants were recruited for the experiment. Initial contact was made with 50 potential participants using the "snowball" technique (Solowij et al. 1992*)* starting from MDMA users and non-users known to the experimenter. A phone survey of the potential participants was conducted using a structured questionnaire on drug use, pain, and depression to ascertain those participants most appropriate for the study. The phone survey was conducted by the researcher (M.C.O'R.), who is a registered nurse and was a final year psychology student. Participants were asked if they had ever used the following substances; caffeine, nicotine, alcohol, cannabis, solvents, acid, cocaine, heroin and ecstasy. Participants were given the opportunity to mention any other drugs they had used for recreational (i.e. not prescribed) purposes. For all drugs apart from ecstasy, participants who had responded positively were asked how regularly they used each drug. "Regularly" was defined as ingestion of drug at least once a month, or more. Those participants identified as using ecstasy were asked further questions related to frequency and duration of use, to detail their pattern of consumption. Any participants with a history of chronic pain or depression were not considered for the study.

Completed questionnaires were compared to assess polydrug use other than MDMA. This allowed for the selection of two groups who were matched for regular use of psychoactive drugs other than ecstasy. Fifteen polydrug users who used MDMA and ten polydrug users who did not use MDMA were selected for the experiment. All participants in the MDMA group were long-term users (minimum 2 years) with an average lifetime consumption of between 200 and 300 tablets. The average age of participants was 29.5±3.8 years (mean±SD) (range; 23–38). All participants completed the experiment and were not paid for their time.

Materials

A structured questionnaire was developed to establish participant's drug, pain, and depression histories. The Nowlis Mood Adjective checklist (Nowlis 1965) was used to obtain a rating for mood on the day of the experiment. This listed 12 feelings or moods and the participants rated how accurately each one described their mood during the day of testing.

Procedure

The participants in the MDMA group contacted the experimenter the day after using MDMA and arranged to attend for testing 3 or 4 days post-ingestion of the drug. The non-MDMA group were also

tested mid-week after a weekend in which they had attended a club. All participants rated their mood on the mood checklist shortly before pain tolerance was tested. Pain tolerance was determined with a cold-pressor test.

The test was done as described by Liebmann et al. (1994). The participant immersed their dominant hand up to wrist level for 2 min in a waterbath at 37°C, and thereafter in an ice-cold waterbath maintained at 3–4°C. The ice was manually stirred during the test to ensure coldness on the skin. The subject was instructed to keep their hand in water until the discomfort level rose to a point at which they felt the need to remove their hand. A stopwatch was used to record in seconds how long the subject kept their hand in water, which was seen as a measurement of pain tolerance. All testing was carried out in the same quiet room and the experimental procedure (mood questionnaire and cold-pressor test) took no more than 10 min in total.

Results

Participants in both groups were well matched on their use of alcohol, nicotine, solvents, cocaine and heroin and closely matched on their use of cannabis and acid. With the exception of nicotine and caffeine, none of the participants had used any drugs on the day of testing. Table 1 shows the pattern of drug use among the 25 participants.

Table 2 shows the mean (±SD) pain tolerance in seconds recorded for each group. Since the number of participants was small and the two groups were unequal in size, a Mann-Whitney *U*-test was used for analysis. The non-MDMA group immersed their hands in cold water for an average of 24.3 s longer than participants in the MDMA group. This difference was found to be significant (U=39.00, N_1=10, $N_{2=}$15, P=0.023 one-tailed).

Table 1 MDMA and non-MDMA groups were matched for usage of other recreational drugs. List of other drugs consumed by each group either regularly or ever

Pattern of drug use among participants				
	MDMA users (n=15)		Non-MDMA users (n=10)	
	Ever*	Regular**	Ever	Regular
Caffeine	15	15	10	8
Nicotine	15	11	9	8
Alcohol	15	13	10	8
Cannabis	15	9	8	7
Solvents	6	0	3	0
Acid	8	2	5	3
Cocaine	13	10	7	6
Heroin	5	0	2	0

* Participant has tried the drug at least once but does not take regularly

** Participant takes the drug at least once a month

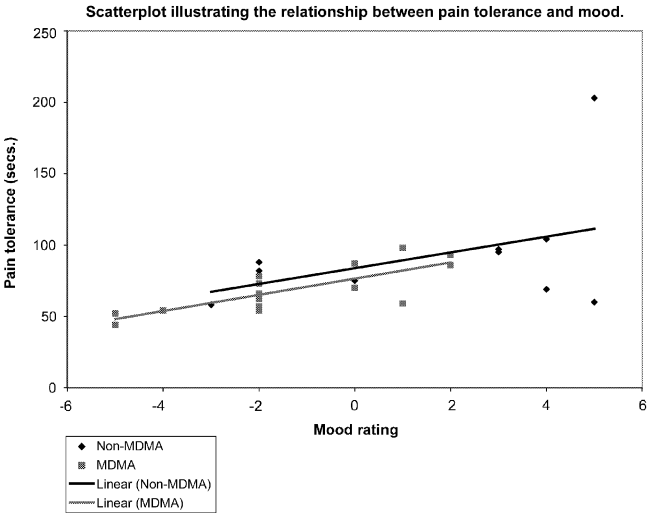

Fig. 1 Scatter plot to illustrate the relationship between mood rating and pain tolerance (s) in both the non-MDMA and MDMA groups. There was a significant positive correlation for all the participants combined (rho=0.617, n=25, P<0.0005, two-tailed) and for the MDMA group (rho=0.796 n=15, P<0.0005, two-tailed) but not for the non-MDMA group on its own (rho=0.350, n=10, P=0.322 two-tailed)

Scores from the Nowlis mood checklist yielded ordinal data ranging from +5 to − 5. +5 was the highest positive mood rating obtainable while −5 was the most negative mood rating obtainable. One overall score was obtained for each participant. As the ordinal data from the mood checklist was ranked a Mann-Whitney *U*-test was used for analysis. There was a significant difference in mood between the MDMA and the non-MDMA group (U=35.00, N_1=10, $N_{2=}$15, P=0.012 one-tailed). Participants in the non-MDMA group rated their mood as more positive (mean=1.70) than participants in the MDMA group (mean=−1.3).

For all the participants in the study there was a significant positive correlation between mood and pain tolerance (rho=0.617, n=25, P<0.0005 two-tailed). Correlations between pain tolerance and mood for each experimental group are shown in Fig. 1.

There was no significant correlation between mood and pain tolerance in the non-MDMA group (rho=0.350, n=10, P=0.322 two-tailed). There was a significant positive correlation between mood and pain tolerance in the MDMA group (rho=0.796 n=15, P<0.0005, two-tailed).

Table 2 Mean (±SD) pain tolerance in seconds (determined using the cold-pressor test) for the non-MDMA and MDMA groups, 3–4 days after most recent usage. Also shown is the group mean mood rating scores determined from the Nowlis Mood Adjective checklist, administered shortly before the pain tolerance test

	MDMA users	Non-MDMA users	P-value
Pain tolerance mean (SD)	68.8 (16.4)	93.10 (41.6)	0.023 one-tailed
Mood rating mean (SD)	–1.3 (2.3)	1.7 (3.12)	0.012 one-tailed

Discussion

This study postulated that because 5-HT is implicated in nociception and because alterations in 5-HT function have been associated with MDMA use, pain measures may be altered in MDMA users. The non-MDMA group was able to immerse their hands in the cold water for a significantly longer time than the MDMA group. This supports the postulated decreases in pain tolerance among MDMA users suggested by this study.

Previous research by McCann et al. (1994) failed to find differences in nociceptive responses to ischaemic pain. There were, however, fundamental differences between the studies, which may account for the conflicting results. Participants in McCann's study had on average last used MDMA 18 weeks prior to study participation, with some participants abstaining from MDMA for as long as 2 years. They rationalised that the possible lack of significant findings was secondary to serotonergic axonal recovery at the level of those brain structures that modulate pain. This theory, although plausible in view of animal studies, which have shown regeneration of the axons damaged by MDMA (Fischer et al. 1995), would not apply to the current results. Critically, the results from this study were obtained from participants who regularly use MDMA, and all participants had consumed the drug three or four days prior to testing.

In recent animal research, Morley-Fletcher et al. (2002) found that acute administration of MDMA induced a dose-dependent reduction in pain sensitivity in mice. This was expected considering the large increases in serotonin levels that follow MDMA administration. They proposed a role for 5-HT in this process and concluded that differences in sensitivity to MDMA found in the three age groups of adolescent mice tested could be accounted for by a differential degree of maturation of the serotonergic system. This claim was supported with evidence that estimates of 5-HT turnover in the striatum area have been reported to be approximately 4-fold lower in middle adolescent rats relative to adult animals (Teicher and Andersen 1999). These findings support the assumption of this research that the decreases in pain tolerance found among MDMA users were serotonergically mediated.

Results from this study support previous research (Curran and Travill 1997) that found lower mid-week mood among MDMA users as compared with a control group. The acute euphoric effects of this drug are very different from the low mood often experienced a few days later; however, neither may reflect possible neurotoxic effects. Many regular MDMA users report that the positive effects of the drug decrease over time, whilst the more negative aspects increase in frequency. This could suggest neurotoxicity rather than neuroadaption, as the acute effects of MDMA are finished within a few hours (Merrill 1996). However, differences in reported experiences over time may equally reflect "psychological tolerance" derived from repeated exposure to the psychoactive effects of the drug and consequent changes in the expectations of users (Curran 2000). Another possibility, which cannot be ignored when interpreting the differences in mood between groups, is that after the MDMA "high" at the weekend, people may be more likely to feel comparatively "low" on a normal weekday regardless of any disruption to serotonin levels. Future research attempting to draw stronger conclusions about the presence of persistent depressed mood after ecstasy use need to employ more specific measures of depression with larger samples over longer periods of time.

An overall positive correlation was found in this study between mood and pain tolerance. Research has indicated that mood can mediate the effect of pain with Weisenberg et al. (1998) demonstrating increases in pain tolerance associated with increases in positive mood. Such results suggest that positive mood may induce physiological changes that affect the sensory components of pain. So in the absence of any possible impairment to the body's pain modulation system as a result of MDMA use, the more positive rating for mood in the non-MDMA group would be expected to correspond to higher measurements of pain tolerance. This is indeed what was observed, and the negative mood reported by the MDMA users was associated with a lower mean measurement of pain tolerance. Further analysis, however, revealed that when pain tolerance and mood were correlated for each individual group, no correlation was found among the non-MDMA users while a positive correlation of 0.8 was observed among the MDMA group. Although the authors acknowledge that the lack of a significant correlation in the non-MDMA group may be an artefact of its smaller sample size, it could also be interpreted as evidence that MDMA is implicated in serotonin mediated alterations to the body's ability to modulate pain.

The MDMA users engaged in this study had an estimated lifetime consumption of between 200 and 300 tablets and all were long-term users (minimum 2 years). They also reported using the drug on average 3 times a month. This means that participants in the MDMA group had approximately one sleepless night every 10 days. One night's sleep "shift" is able to cause distinctive aberration of circadian rhythm. The participants in this and nearly all of the previous research were therefore in the situation of permanent nightsleep deprivation. It is known that the lack of natural night sleep can exacerbate/aggravate depressive states and cause changes in the biochemistry of the brain. Future research needs to address the effect of chronic night sleep deprivation/disturbance over periods of many years if the effects of MDMA are to be successfully isolated. The non-MDMA group were firstly approached in a club environment, so were likely to share a similar lifestyle to the MDMA group. Use of a control group of polydrug users (as in this study) is a successful strategy as they are likely to share a more similar lifestyle as compared to a control group of non drug-users.

This study attempted to control for polydrug use by matching groups as closely as possible for drug use, comparing polydrug users who use MDMA with polydrug users who do not use MDMA. This is an improvement on

earlier studies (Parrot and Lasky 1998) that have not attempted to control for the effects of other psychoactive drugs. Future studies should, however, attempt to collect more detailed information relating to previous drug usage especially with regard to the number of times each drug had been used. This would provide data more amenable to statistical analysis facilitating more rigorous comparisons between the two groups. The groups used in the study were well matched for regular use of psychoactive drugs other than ecstasy. This was a successful strategy strengthened by the fact that few recreational drugs outside of the amphetamine class produce selective neurotoxic effects of the type produced by MDMA.

The results from the assessment of mood in this study are supportive of previous research, which has found mid-week depressed moods among MDMA users. This corroborates the link between MDMA use and serotonin. An interesting correlation was found between mood and pain tolerance in the MDMA group, which could be suggestive of 5-HT functional disturbances, but does not necessarily indicate toxicity.

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