The effects of MDMA pre-treatment on behavioural responses to mephedrone in the rat

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Introduction

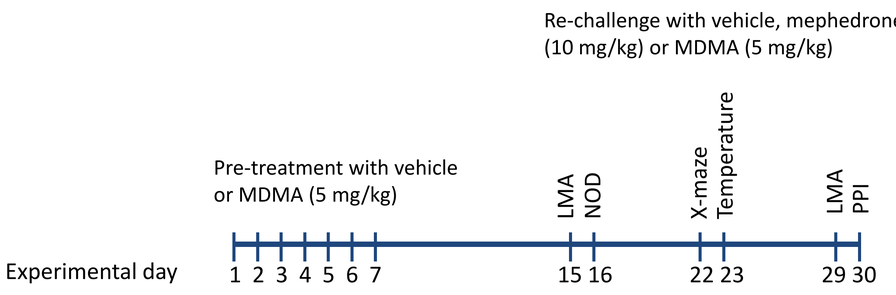
The cathinone derivative, 4-methylmethcathinone (mephedrone), was first introduced to Europe in 2007 as a 'legal high' and since then has received substantial media attention having been implicated in a number of adverse events and deaths which resulted in its reclassification as a controlled substance in many European countries. Before the ban, mephedrone was the most popular of the cathinone derivatives to be used recreationally with users comparing its psychostimulant effects to those of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'; Winstock et al., 2011).

Acutely MDMA releases 5-HT and dopamine from nerve endings and can cause long term neurotoxic damage in the forebrain (Green et al., 2003). It also induces behavioural sensitisation in rats (Aberg et al., 2007). Initial studies investigating the effects of mephedrone in rats have revealed that it also releases neuronal 5-HT and dopamine (Kehr et al, 2011; Baumann et al., 2012). In addition, the majority of mephedrone users (87% of 1506 mephedrone users, mean age=26 years) have previously consumed MDMA (Winstock et al., 2011). This study therefore examined the effects of MDMA pre-treatment on subsequent responses of rats to mephedrone and MDMA using behavioural paradigms regulated by monoamine function.

Methods

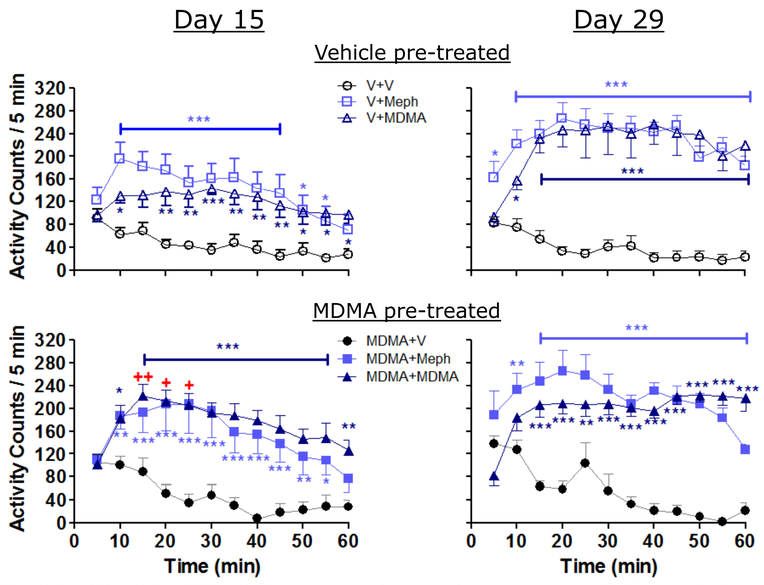
Rats (n=8 per group, 170-205 g) received intraperitoneal (±)-MDMA-HCl (5 mg/kg) or saline vehicle (1 ml/kg; v) pre-treatment once daily for seven days (d 1-7), followed by a seven day rest period (d 8-14), as this protocol has been shown to induce sensitisation in previous studies in other rat strains (Aberg et al. 2007). Rats were subsequently challenged with saline vehicle (1 ml/kg; v+v or MDMA+v), (±)-MDMA-HCl (5 mg/kg; v+MDMA or MDMA+MDMA) or (±)-mephedrone-HCl (10 mg/kg; v+meph or MDMA+meph) on two consecutive days a week for three weeks (d 15, 16, 22, 23, 29 and 30), to mimic weekend-type recreational use in humans. On challenge days, rats were assessed for locomotor activity (LMA, d 15 and 29), novel object discrimination (NOD, d 16), elevated plus maze (x-maze, d 22), rectal and peripheral temperature changes (d 23) or prepulse inhibition of acoustic startle response (PPI, d 30).

Experimental design



Results

MDMA pre-treatment caused sensitisation to LMA effects of MDMA, but not mephedrone



*p<0.05; **p<0.01; ***p<0.001 compared to respective vehicle; +p<0.05; ++p<0.01 compared to v+MDMA, Bonferroni post-hoc following repeated measures ANOVA.

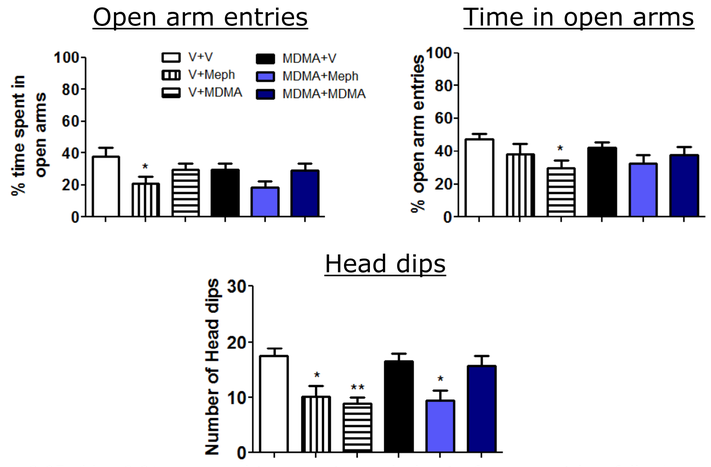
❖ Acute drug challenge increased LMA on d 15 and 29

❖ MDMA pre-treatment increased sensitivity to the challenge dose of MDMA on d 15, but not d 29

❖ Total LMA of v+meph, v+MDMA and MDMA+meph was significantly higher on d 29 than d 15

Results

Mephedrone and MDMA have differential effects in the elevated plus maze, with no evidence of cross sensitisation

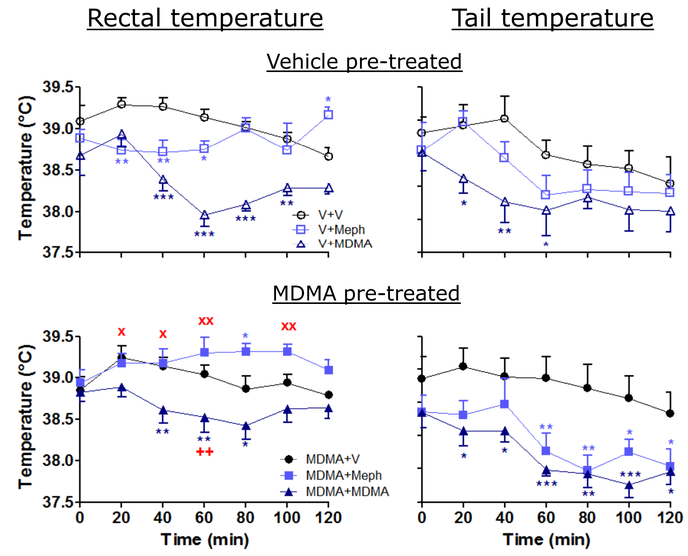


*p<0.05, **p<0.01 compared to respective vehicle, Bonferroni post-hoc following Two way ANOVA

❖ Mephedrone reduced time spent in open arms in vehicle, but not MDMA pre-treated group and also reduced head dips in both groups irrespective of pre-treatment

❖ In contrast, MDMA reduced open arm entries and head dips in vehicle pre-treated groups only

MDMA pre-treatment has differential effects on mephedrone-induced changes in rectal and tail temperature



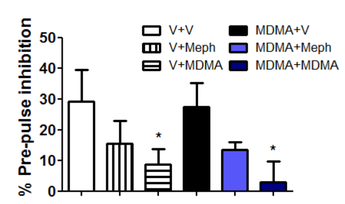
*p<0.05, **p<0.01, ***p<0.001 compared to respective vehicle; ++p<0.01 compared to v+MDMA; xp<0.05, xxp<0.01 compared to v+meph, Bonferroni post-hoc following Two way repeated measures ANOVA

❖ Mephedrone decreased rectal and tail temperature following vehicle pre-treatment

❖ MDMA pre-treatment abolished mephedrone-induced hypothermia

❖ MDMA challenge decreased rectal and tail temperature in both vehicle and MDMA pre-treated rats

MDMA reduced % prepulse inhibition following the 80 dB prepulse



*p<0.05 compared to respective vehicle, Bonferroni post-hoc following Two way ANOVA

❖ There was a prepulse x treatment interaction effect so startle response to 80 dB was analysed independently of the other prepulses, as this is the most sensitive to changes in PPI

❖ MDMA significantly reduced % PPI at 80 dB following vehicle and MDMA pre-treatment

Mephedrone and MDMA had no significant effect on novel object discrimination

There was no significant treatment x object interaction in the choice trial of NOD ($F(2,42)=1.631$, $p>0.05$), nor any significant effect of treatment on the discrimination ratio ($p>0.05$).

Conclusions

The initial LMA test revealed sensitisation of MDMA pre-treated animals to MDMA. Subsequent testing suggested additional sensitisation of vehicle pre-treated animals to MDMA across the challenge phase. Sensitisation to mephedrone is evident on day 29 compared to 15 but this is not caused by MDMA pre-treatment as it occurs in both pre-treatment groups. In contrast, there is evidence for possible cross-tolerance between MDMA and mephedrone on rectal temperature. Despite similar effects of mephedrone and MDMA on anxiety and cognition (suggesting similar mechanisms of action) there was no evidence of cross-sensitisation between these two drugs.

References

Aberg et al., 2007. Neurotoxicol Teratol. **29**, 37-46
Baumann et al., 2012. Neuropsychopharmacol. **37**, 1192-1203
Green et al., 2003. Pharmacol. Rev. **55**, 463-508
Winstock et al., 2011. Addiction **106**, 154-161

Acknowledgements

This study was funded by the University of Nottingham, School of Biomedical Sciences. There is no conflict of interest to report.