Behavioral Sensitization Following Concurrent Exposure to Mephedrone and d-Amphetamine in Female Mice

Michael D. Berquist II, M. Melissa Peet, Lisa Baker
Western Michigan University, Kalamazoo MI 49008

Introduction

- Mephedrone (4-methylmethcathinone) is an active constituent of the illicit designer drugs commonly known as “bath salts”. In recent years, the recreational use and abuse of mephedrone and related synthetic methcathinones have dramatically increased in popularity in the U.S. and U. K. (e.g., Dybdal-Hargreaves et al., 2013; Winstock et al., 2010).
- Mephedrone consumption is associated with a number of adverse side effects such as palpitations, bruxism, agitation (Winstock et al., 2011; Wood et al., 2010; Dargan et al., 2010), paranoia, hallucinations, aggressive/violent behavior, excited delirium, and psychosis (Ross et al., 2012).
- Mephedrone may facilitate deleterious effects of other drugs of abuse if consumed concurrently (e.g., Angoa-Perez et al., 2013).
- The current study investigated abuse liability of a mixture of mephedrone and d-amphetamine using a behavioral sensitization paradigm in female mice.

Methods

Subjects: Thirty female CD-1 mice (20-28g).

Apparatus: Eight custom-built Plexiglas chambers (40 cm x 40 cm x 40 cm) housed within activity monitoring system (Accuscan Instruments, Columbus, OH). Activity was monitored by infrared beam breaks and several measures of activity were determined using Versamax® software.

Drugs: *d*-amphetamine hemisulfate (1 mg/kg), mephedrone-hydrochloride (3 mg/kg) were dissolved in 0.9% saline and administered in a volume of 10 ml/kg by subcutaneous injection.

Procedure:

•Four treatment groups (n=6-8) randomly assigned to saline, amphetamine, mephedrone, or amphetamine + mephedrone

•Day 1 and Day 8: Habituated to test chambers for 30 min, followed by injection and activity monitoring for 60 min.

•Days 3-7: Animals dosed daily with respective compounds, no activity monitoring.

•Days 9-18: No injections given (10-day washout period).

•Day 19: Habituated to chambers for 30 min, followed by 1 mg/kg d-amphetamine and activity monitored for 60 min.

Data Analysis: Horizontal activity and stereotypy measures compared among treatment groups and between days 1 and 8. All data were analyzed using GraphPad Prism 4.0.

Results

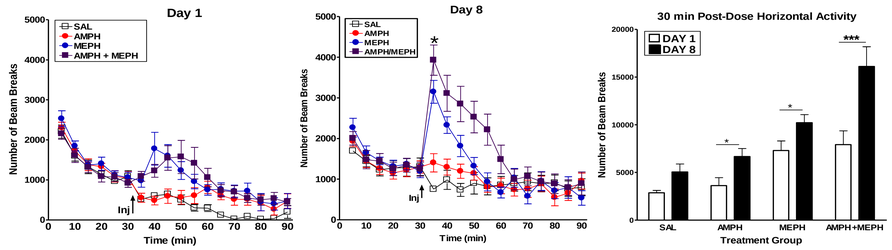

Figure 1. Horizontal activity 30 min before and 60 min after SAL, AMPH, MEPH, or AMPH+MEPH injections on day 1 (left) and day 8 (middle). Total horizontal activity 30 min post-dose on day 1 and day 8 (right).

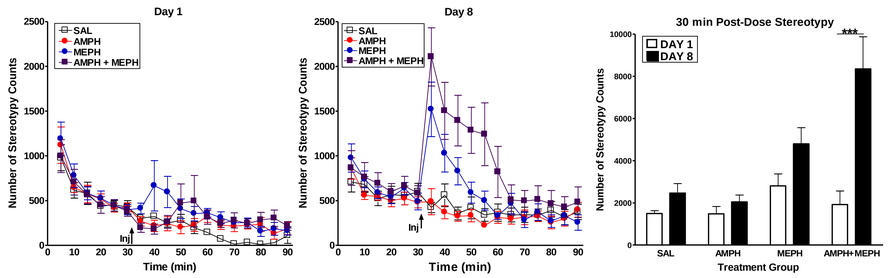

Figure 2. Stereotypy 30 min before and 60 min after drug administration on day 1 (left) and day 8 (middle). Total stereotypy 30 min post-dose on day 1 and day 8 (right).

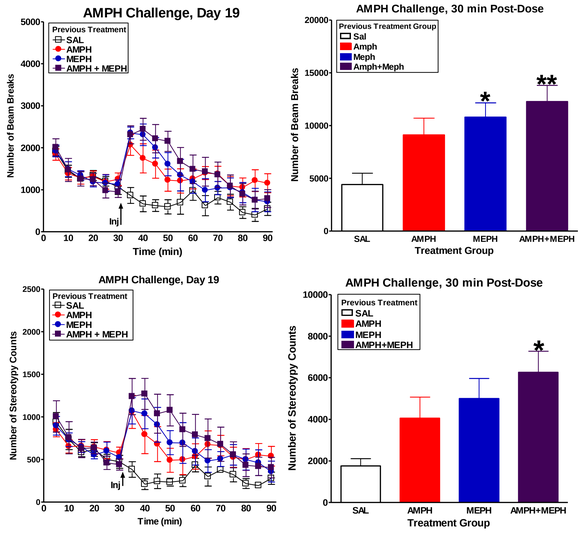

Figure 3. Following a 10-day washout period, AMPH increased horizontal activity and stereotypy to a greater extent in mice previously exposed to repeated MEPH or AMPH+MEPH treatments compared to those exposed to repeated SAL or AMPH treatments.

Results

- A two way ANOVA on 30 min post-dose horizontal activity showed a significant treatment effect ($F(3,26) = 11.70$, $p < 0.001$), a significant test day effect ($F(1,26) = 56.33$, $p < 0.001$), and a significant treatment x test day interaction ($F(3,26) = 6.72$, $p < 0.01$). Significant post-tests: *p < 0.05, ***p < 0.001 (figure 1, right).
- A two-way ANOVA on 30 min post-dose stereotypy showed a significant treatment effect ($F(3,26) = 7.02$, $p < 0.01$), significant test day effect ($F(1,26) = 30.16$, $p < 0.001$), and a significant treatment x test day interaction ($F(3,26) = 9.30$, $p < 0.001$). Significant post-tests: ***p < 0.001 (figure 2, right).
- One way ANOVAs comparing treatment groups on 30 min post-dose horizontal activity ($F(3, 26) = 4.92$, $p < 0.01$) and stereotypy ($F(3, 26) = 3.70$, $p < 0.05$) following AMPH treatment were statistically significant. Significant post-tests: *p < 0.05, ** p < 0.01. (figure 3, right).

Conclusions

- The current findings indicate that concurrent administration of moderately low doses of AMPH + MEPH produced greater behavioral sensitization than either drug alone in female mice. These results are consistent with previous findings in male rats. (e.g., Gregg et al., 2013; Lisek et al., 2012)
- The risk for abuse with MEPH may be enhanced when combined with other psychostimulants. Further research on the abuse liability of drug mixtures are warranted.

References

Angoa-Perez, M., Kane, M. J., Briggs, D. I., Francescutti, D. M., Sykes, C. E., Shah, M. M., Thomas, D. M., & Kuhn, D. M. (2013). Mephedrone does not damage dopamine nerve endings of the striatum, but enhances the neurotoxicity of methamphetamine, amphetamine, and MDMA. *Journal of Neurochemistry, 125*, 102-110.

Dargan, P. I., Albert, S., & Wood, D. M. (2010). Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *Quarterly Journal of Medicine, 103*, 875-879.

Dybdal-Hargreaves, N.F., Holder, N. D., Ottoson, P. E., Sweeney, M. D., & Williams, T. (2013). Mephedrone: Public health risk, mechanisms of action, and behavioral effects. *European Journal of Pharmacology, 714*, 32-40.

Gregg, R. A., Tallarida, C. S., Reitz, A., McCurdy, C., & Rawls, S. M. (2013). Mephedrone (4-methylmethcathinone), a principal constituent of psychoactive bath salts, produces behavioral sensitization in rats. *Drug and Alcohol Dependence, 133*, 746-750.

Lisek, R., Xu, W., Yuvasheva, E., Chiu, Y., Reitz, A. B., Liu-Chen, L., & Rawls, S. M. (2012). Mephedrone (‘bath salt’) elicits conditioned place preference and dopamine-sensitive motor activation. *Drug and Alcohol Dependence, 126*, 257-262.

Ross, E. A., Reisfield, G. M., Watson, M. C., Chronister, C. W., & Goldberger, B. A. (2012). Psychoactive “bath salts” intoxication with methylenedioxypyrovalerone. *The American Journal of Medicine, 125*, 854-858.

Wood, D. M., Greene, S. L., & Dargan, P. I. (2010). Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emergency Medicine Journal , 28*, 280-282.

Winstock, A., Mitcheson, L., Ramsey, J., Davies, S., Puchnarewicz, M., & Marsden, J. (2011). Mephedrone: Use, subjective effects and health risks. *Addiction, 106*, 1991-1996.

Winstock, A. R., Mitcheson, L. R., Deluca, P., Davey, Z., Corazza, O., & Schifano, F. (2010). Mephedrone, new kid for the chop? *Addiction, 106*, 154-161.