Gender differences in the cardiovascular actions of stimulants in the rat.

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We have previously shown that the cardiovascular actions of the stimulants cathinone and methylenedioxymethamphetamine (MDMA) in the anaesthetised rat are largely indirect by the release of noradrenaline (Alsufyani & Docherty, 2015). Most published pharmacological studies of stimulants have employed male animals. Hence, in this study, we have chosen to investigate possible gender differences in the cardiovascular actions of the stimulants cathinone, MDMA and ephedrine in comparison with the archetypal indirect sympathomimetic agent tyramine.

Male and female Wistar rats (190-300g) were anaesthetized with pentobarbitone (60mg/kg, i.p., and maintenance doses, as required, i.v.). Studies were approved by the Health Products Regulatory Agency (Ireland) and by the RCSI Research Ethics Committee. Some rats were sympathectomised with 6-hydroxydopamine (40 mg/kg i.p., on day 1 and on day 2, 3 or 4; used on the following day). In anaesthetized rats, dose-response curves were obtained to test drugs given i.v. Data is presented as mean±S.E.M., from n animals, and analysis was performed using ANOVA and Dunnett's test.

In anaesthetised male and female rats, tyramine produced marked pressor responses with similar maximum increases in diastolic blood pressure in both female (60.1±7.7 mmHg, n=8) and male (53.3±4.4 mmHg, n=8) rats. MDMA (1mg/kg) produced small pressor responses, and cathinone and ephedrine had mixed pressor and depressor effects. In sympathectomised rats, the tachycardia to cathinone or MDMA was markedly attenuated (P<0.05), but the tachycardia to ephedrine and tyramine was partly resistant. The blood pressure effects of tyramine were also markedly attenuated by sympathectomy. Cathinone, MDMA, tyramine (all 0.001-1 mg/kg) and ephedrine (0.001-10 mg/kg) produced marked tachycardia: the potency (pED₅₀, -log mg/kg) of tyramine (male: 0.43±0.16, n=8, or 0.27 mg/kg; female: 0.92±0.15, n=8, or 0.83 mg/kg, P<0.05) was significantly greater in male rats, and the ephedrine maximum tachycardia but not potency was also significantly greater in male rats (P<0.05).

Comparing male and female rats, there were no differences in pressor responses to any agent, and no differences in the tachycardia to cathinone or MDMA. However, both ephedrine and tyramine produced a significantly greater tachycardia in male than in female rats.

The results demonstrate that there are gender differences in cardiac actions for ephedrine and tyramine but not for cathinone and MDMA. Differences between stimulants may reflect different modes of action, between effects at the noradrenaline transporter, the vesicular transporter and between direct and indirect actions. Indirectly acting agents such as cathinone and MDMA, that act mainly on the noradrenaline transporter do not show gender differences, whereas agents such as tyramine and ephedrine that act at least partly on the vesicular transporter or have direct components to their actions show increased responsiveness in male rats.
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