Sprague–Dawley rats display metabolism-mediated sex differences in the acute toxicity of 3,4- methylenedioxymethamphetamine (MDMA, Ecstasy)

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The use of the amphetamine derivative 3,4- ethylendioxymethamphetamine (MDMA, Ecstasy) has been associated with unexplained deaths. Male humans and rodents are more sensitive to acute toxicity than females, including a potentially lethal hyperthermia. MDMA is highly metabolized to five main metabolites, by the enzymes CYP1A2 and CYP2D. The major metabolite in rats, 3,4-methylenedioxyamphetamine (MDA), also causes hyperthermia. We postulated that the reported sex difference in rats is due to a sexual dimorphism(s). We, therefore, determined (1) the LD50 of MDMA and MDA, (2) their hyperthermic effects, (3) the activities of liver CYP1A2 and CYP2D, (4) the liver microsomal metabolism of MDMA and MDA, (5) and the plasma concentrations of MDMA and its metabolites 3 h after giving male and female Sprague–Dawley (SD) rats MDMA (5 mg/kg s.c.). The LD50 of MDMA was 2.4-times lower in males than in females. MDMA induced greater hyperthermia (0.9 °C) in males. The plasma MDA concentration was 1.3-fold higher in males, as were CYP1A2 activity (twice) and N-demethylation to MDA(3.3-fold), but the plasma MDMA concentration (1.4-fold) and CYP2D activity (1.3-fold) were higher in females. These results suggest that male SD rats are more sensitive to MDMA acute toxicity than are females, probably because their CYP1A2 is more active, leading to higher N-demethylation and plasma MDA concentration. This metabolic pathway could be responsible for the lethality of MDMA, as the LD50 of MDA is the same in both sexes. These data strongly suggest that the toxicity of amphetamine-related drugs largely depends on metabolic differences.

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