

052P ACTIONS OF AMPHETAMINE DERIVATIVES AND CATHINONE AT THE NORADRENALINE TRANSPORTER

Linda Cleary & James R Docherty. Department of Physiology, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland

We have recently shown that MDMA, MDA, cathinone and to a lesser extent MDEA share with cocaine an ability to potentiate the contractile actions of noradrenaline (NA) but not isoprenaline in the 1Hz paced rat right ventricle (Cleary *et al.*, 2002). It was concluded that these drugs, like cocaine, prevented the reuptake of noradrenaline into nerve terminals, an action which could account for the cardiovascular complications associated with MDMA abuse. The purpose of this study was to directly test the actions of these compounds at the NA transporter.

Male Wistar rats (250 - 300g) were killed by CO₂ overdose and their hearts were quickly removed. For inhibition of [³H]-NA uptake, left ventricular slices were incubated for 15 minutes at 37°C in oxygenated Krebs with [³H]-NA 25nM and increasing concentrations of amphetamine derivatives. Non specific uptake was determined at 4°C. Displacement of [³H]-Nisoxetine Binding to the NA transporter was measured by incubating rat cerebral cortex membranes for 4 hours at 4°C with [³H]-nisoxetine 2nM and increasing concentrations of amphetamine derivatives. Non specific binding was determined in the presence of desipramine 0.3 µM.

Total specific [³H]-NA uptake was 43.5±2.6 fmol/mg/15min (n=24). All these compounds inhibited uptake of [³H]-NA. Potency (- log EC₅₀) values were: cocaine 6.16±0.15, cathinone 6.03±0.16, MDMA 6.05±0.07, MDA 5.68±0.06 and MDEA 5.56±0.08. Cocaine, cathinone and MDMA were significantly more potent than MDEA. MDA was

potent than MDMA and cocaine. Test agents all displaced [³H]-nisoxetine binding at the rat cerebral cortex NA transporter. MDMA was the least potent at displacing [³H]-nisoxetine binding; - log EC₅₀ values: Cocaine 5.04±0.08, Cathinone 5.40±0.14, MDA 4.66±0.11, MDEA 4.99±0.15, MDMA 4.22±0.07.

In rat right ventricular strips, NA increased 1Hz stimulation-evoked contractions with a pD₂ of 7.45±0.12 (n=25). Cocaine, MDMA, MDA and cathinone (all 10µM) significantly increased the potency of NA to 6.25±0.11, 6.48±0.13, 6.17±0.05 and 6.27±0.10, respectively, as compared with the effects of vehicle (5.42±0.08) MDEA 10µM had no effect although 100µM caused a significant increase.

In NA uptake studies, MDEA was the least potent and also had low potency functionally in the paced right ventricle. In [³H]-nisoxetine displacement studies, MDMA was significantly less potent than the other drugs but not in functional studies. Other studies report a poor correlation between inhibition of binding and inhibition of uptake at the NA transporter (Eshleman *et al.*, 1999). In conclusion, cardiac actions of amphetamine derivatives may involve competitive blockade of the NA transporter. This action may result in cardiac morbidity as previously shown for cocaine.

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Cleary, L. *et al.* (2002) *Eur. J. Pharmacol.* 451, 303-308.
Eshleman A.J. *et al.* (1999) *J. Pharmacol. exp. Ther.* 289, 877-885.