Society for Neuroscience Abstracts, 24, 341.8 (1998)

Methcathinone and 2-methylamino-1-(3,4-methylenedioxyphenyl) propan-1-one (methylone) selectively inhibit plasma membrane catecholamine reuptake transporters.

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Abstract

Methcathinone, the benzylic ketone analog of methamphetamine (MA), and methylone, the benzylic ketone analog of 3,4-methylenedioxymethamphetamine (MDMA), were synthesized and tested for their abilities to inhibit monoamine uptake *in vitro*. Methcathinone and methylone were threefold less potent than MA or MDMA at inhibiting [^{3}H]5-HT uptake into human platelets, with IC_{50}'s of 31.4 ± 7.3 uM and 5.8 ± 0.7 uM, respectively. In C6 glial cells stably expressing the rat dopamine transporter, methcathinone and methylone were similar in potency to MA and MDMA, with IC_{50}'s for [^{3}H]DA uptake of 0.36 ± 0.06 uM and 0.82 ± 0.17 uM, respectively. Methcathinone and methylone were also similar in potency to MA and MDMA in C6 cells expressing the human norepinephrine transporter, with IC_{50}'s for [^{3}H]NE accumulation of 0.51 ± 0.10 uM and 1.2 ± 0.1 uM, respectively. The benzylic ketone moiety of methcathinone and methylone had a large (tenfold) negative impact on the abilities of these drugs to inhibit the vesicular monoamine transporter (VMAT2) compared to MA and MDMA. In VMAT2-containing bovine chromaffin granules, the IC_{50}'s for [^{3}H]5-HT uptake were 103 ± 15 uM for methcathinone and 125 ± 16 uM for methylone. These results indicate that methcathinone and methylone are potent and selective inhibitors of plasma membrane catecholamine reuptake transporters, with more modest effects at the serotonin reuptake transporter. These drugs are essentially inactive at the vesicular monoamine transporter.