

***N,N*-dimethyl-thioamphetamine and methyl-thioamphetamine, two non-neurotoxic substrates of 5-HT transporters, have scant *in vitro* efficacy for the induction of transporter-mediated 5-HT release and currents**

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Abstract

We studied two non-neurotoxic amphetamine derivatives (methyl-thioamphetamine, MTA and *N,N*-dimethylMTA, DMMTA) interacting with serotonin (5-HT) transporters (SERTs) with affinities comparable to that of *p*-Cl-amphetamine (pCA). The rank order for their maximal effects in inducing both [³H]5-HT release from rat brain synaptosomes or hSERT-expressing HEK-293 cells, and currents in hSERT-expressing oocytes, was pCA » MTA ≥ DMMTA. A correlation between drug-induced release and currents is also strengthened by the similar bell shape of the dose–response curves. Release experiments indicated that MTA and DMMTA are SERT substrates although MTA is taken up by HEK-293 cells with a $V_{\max}$ 40% lower than pCA. The weak effects of MTA and DMMTA *in vitro* might therefore be due to their properties as ‘partial substrates’ on the mechanisms, other than translocation, responsible for currents and/or release. After either local or systemic *in vivo* administration, MTA and DMMTA release 5-HT in a manner comparable to pCA. These findings confirm that the neurotoxic properties of some amphetamine derivatives are independent of their 5-HT-releasing activity *in vivo*. It is worth noting that only those amphetamine derivatives with high efficiency in inducing 5-HT release and currents *in vitro* have neurotoxic properties.