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Improving Amphetamine Therapeutic Selectivity: N,N-dimethyl-MTA has Dopaminergic Effects and does not Produce Aortic Contraction

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Abstract: Amphetamine derivatives have therapeutic potential in diseases such as attention deficit hyperactivity disorder, narcolepsy and obesity. However, their prolonged use has been associated with cardiovascular toxicity and addiction. In recent years, we have studied the pharmacological effects of amphetamine derivatives such as methylthioamphetamine (MTA) and *N*,*N*dimethyl-thioamphetamine, with the aim of improving their therapeutic selectivity. In this work, we show that similarly to MTA, *N*,*N*-dimethyl-thioamphetamine has effects on the dopamine system, producing a significant increase in extracellular levels of dopamine (as measured by *in vivo* brain microdialysis) and locomotor activity, which is a behavioural measure of dopaminergic activation. However, unlike MTA, *N*,*N*-dimethyl- thioamphetamine does not produce aortic contraction *in vitro*. Our results show that *N*,*N*-dimethyl-thioamphetamine is a drug that retains the dopaminergic effects of amphetamine derivatives but exhibits a lower potential for producing cardiovascular side effects.

Amphetamine and some of its derivatives are psychostimulant drugs whose main mechanism of action is the release of monoamines [1–3]. These drugs have been used in diseases such as attention deficit hyperactivity disorder (ADHD) [4], narcolepsy [5,6] and obesity [7,8]. However, side effects such as cardiovascular toxicity [9–11] and drug dependence [12] have been reported with the prolonged use of amphetamine derivatives.

The interest of our group has been to develop and/or evaluate new amphetamine derivatives with improved pharmacological profiles and their characterization through *in vitro*, *in vivo* and *in silico* methodologies. For instance, 4-methylthioamphetamine (MTA) is a potent, non-neurotoxic serotonin (5-HT) releasing agent [13,14], which also inhibits monoamine oxidase-A [15] and induces aortic contraction *via* noradrenergic mechanisms [16]. All of these effects might account for the toxicity observed in human beings after recreational use of MTA, particularly at high doses [17,18]. Recently, we demonstrated that MTA also produces an increase in extracellular levels of dopamine (DA), an effect which is mediated by the dopamine transporter (DAT) [19]. In the same study, we observed that the administration of MTA produces the activation of dopaminergic neurons in nucleus accumbens (NAc) and striatum [19].

In 2008, we characterized a dimethylated derivative of MTA (N,N-dimethyl-MTA) and found that this drug increases extracellular 5-HT levels by blocking the 5-HT transporter (SERT) [20]. In addition, we have previously shown that N,N-dimethyl-MTA is about 10 times less potent than MTA as a MAO-A inhibitor [21].

In the present work, we focused upon the dopaminergic effects of N,N-dimethyl-MTA. Specifically, our goal was to evaluate the activation of the dopaminergic system by N,N-dimethyl-MTA, through the assessment of brain DA release and locomotor activity (a behaviour associated with increased DA release in the mesocorticolimbic circuit). Furthermore, we studied the ability of N,N-dimethyl-MTA to produce aortic contraction and whether this effect is similar to that described for MTA [16].

Methods

Animals. Male Sprague-Dawley rats weighing 250–280 g, average age 75 days, were used. All experimental procedures were approved by the Ethics Committee of the Faculty of Biological Sciences at the Pontificia Universidad Católica de Chile, Faculties of Science and

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Animals and reagents.

Pharmacy at the Universidad de Valparaóso and the Institutional Animal Experimentation Ethics Board and the Science Council (FONDECYT) of Chile. Efforts were made to minimize the number of animals used and their suffering.

Reagents. (\pm) -MTA and (\pm) -*N*,*N*-dimethyl-MTA hydrochlorides were synthesized as previously reported [21]. (*R*)-(-)-Phenylephrine hydrochloride and citalopram hydrobromide were purchased from Tocris Bioscience (Ellisville, MO, USA). Dopamine standard, EDTA and 1-octanesulfonic acid were purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA). All other reagents were of analytical grade.

In vivo microdialysis. The animals were anaesthetized deeply with choral hydrate (400 mg/kg, i.p.). Body temperature of the animals was maintained at 37°C with an electrical blanket controlled by a thermostat. A quarter of the initial dose of choral hydrate was given every hour to maintain the animal anaesthetized during the course of the experiments. Concentric brain microdialysis probes, 2 mm in length (CMA 12, CMA Microdialysis AB, Solna, Sweden), were implanted in the lateral septum (LS) using the following co-ordinates according to the rat brain atlas [22]: 0.2 mm anterior to bregma, 0.8 mm lateral and 5.8 mm ventral to brain surface. We decided to study the effects of N,N-dimethyl-MTA in the LS as this region is part of the mesocorticolimbic circuit [23] and receives a significant dopaminergic input from the ventral tegmental area (VTA) [24]. The LS has been considered a relay station for cognitive and emotional information involved in several neuropsychiatric pathologies [25] and neurochemical response to drugs of abuse [26,27]. In addition, the effects of local administration of MTA have been evaluated in this region, and therefore, it was suitable for a comparative study. Krebs-Ringer's phosphate buffer (KRP: NaCl 120 mM; KCl 2.4 mM; Na₂HPO₄ 0.9 mM; NaH₂PO₄ 1.4 mM; pH = 7.4) was perfused at 1 µL/min using a Harvard infusion pump (Model 22; Dover, MA, USA). After a stabilization period of 90 min., samples were collected every 20 min. up to 200 min. after the end of the stabilization period. After the fourth basal fraction, N,N-dimethyl-MTA (0.1 or 1 mM) dissolved in KRP was perfused intra-LS during 20 min. In one additional experimental protocol, the effect of intra-LS N,N-dimethyl-MTA (1 mM) was evaluated in the presence of 5-HT uptake blocker. In this case, citalopram (10 µM) was perfused through the cannula during the whole microdialysis procedure. Samples were received in 0.2 M HClO₄ (4 µL), and the extracellular concentration of DA was measured by high-performance liquid chromatography-electrochemical determination (HPLC-ED). In all cases, perfusion samples were maintained on ice during the experiment and stored at -80°C until analysis. At the end of each experiment, animals were killed and brains quickly removed and stored in formalin. Brain sections 50 µm thick were stained with cresyl violet to verify probe location, and the placement of the probe was examined microscopically (fig. 1).

Analysis dialysate samples. High-performance liquid ofchromatography-electrochemical determination of DA was performed as described previously [26]. Briefly, 5 µL of dialysate was injected into a HPLC system (BAS, West Lafayette, IN, USA) with the following configuration: a pump (model PM-80), a SepStick microbore column and an amperometric detector (model LC-4C). The HPLC mobile phase, containing 0.1 M NaH₂PO₄, 1.8 mM 1octanesulfonic acid and 1 mM EDTA (pH adjusted to 2.3), was pumped at a flow rate of 80 µL/min. The potential of the amperometric detector was set at 0.650 V. Under these experimental conditions, retention times were 6.80 min. for DA. Dialysate samples were analysed by comparing their peak area and elution times with reference standards. The detection limit for DA was 0.1 fmol/µL.

Locomotor activity. Basal locomotor activity was measured in control and *N*,*N*-dimethyl-MTA groups as previously described [19]. Briefly, animals were initially habituated to the test cages for 10 min. Immediately after the administration of *N*,*N*-dimethyl-MTA (2.5 or 5.0 mg/kg, i.p.) or saline solution, rats were transferred to test cages ($15 \times 47 \times 26$ cm) equipped with two pairs of infrared lights placed 2.5 cm above the floor. Cross-overs in the test cage were monitored every 1 min. during 90 min., using a counting device programmed to count only when both infrared light beams were interrupted consecutively.

Preparation of rat aorta rings and recording. Rats were killed by stunning, followed by cervical dislocation, and the descending thoracic aorta was quickly isolated and mounted in a tissue chamber as previously described [28]. Briefly, the aorta was dissected into rings of approximately 5 mm in length and then mounted in a tissue bath (Myobath II, WPI, Sarasota, FL, USA), attached to a force transducer and placed in Krebs-Henseleit modified (KHM) buffer containing (mM): NaCl 122.0, KCl 4.7, KH2PO4 1.2, MgCl2 1.2, CaCl2 2.0, NaHCO₃ 15.5, D-(+)-glucose 11.5, EDTA 0.026, pH = 7.4 oxygenated continuously with 95% O2/5% CO2 gas and maintained at 37°C. After an equilibration period of 60 min. under a basal tension of 1.5 g, the viability of each ring was confirmed by contracting the tissue with 70 mM KCl. Changes in isometric tension using cumulative concentrations of phenylephrine, MTA and N,N-dimethyl-MTA $(1 \times 10^{-9} - 1 \times 10^{-3} \text{ M})$ were recorded using Data-Trax2 software (WPI). Aortic contraction is expressed as mg of tension per mg of tissue observed at each concentration of drugs. Phenylephrine was used as reference (EC₅₀ = 8.87×10^{-8} M).

Statistical analysis. In the case of microdialysis studies, femtomoles of DA (uncorrected for recovery) were measured, and values are presented as percentages of basal levels. One-way ANOVA followed by Newman–Keuls post hoc test was used to determine significant differences in the LS DA release after *N*,*N*-dimethyl-MTA perfusion.



Fig. 1. (A) Lateral septum (LS) scheme extracted from the rat brain atlas (Paxinos and Watson) [22]. (B) Typical placement of a microdialysis probe in LS, at 0.2 mm rostrocaudal level from bregma. MS, medial septum; aca, anterior commissure; cc, corpus callosum; LV, lateral ventricle. The arrows show an example of the theoretical position (A) and the real track of a microdialysis probe (B).

In behavioural experiments, data are presented as mean \pm S.E.M. of numbers of horizontal cross-overs, and statistical analysis was performed using one-way ANOVA followed by the Newman–Keuls post hoc test. Data of aortic contraction are presented as mean \pm S.E.M. and were analysed by nonlinear regression analysis and fit to sigmoidal log concentration–response curve. The statistical analyses were carried out with GraphPad Prism v5.0 (GraphPad Software, San Diego, CA, USA).

Results

In vivo microdialysis experiments.

Figure 2 shows the effect of locally perfused N,N-dimethyl-MTA and N,N-dimethyl-MTA plus Citalopram on extracellular levels of DA in the LS. N,N-dimethyl-MTA perfusion (80-100 min.) produced a concentration-dependent increase in extracellular levels of DA in LS. This effect was statistically significant at 1 mM, which was the highest concentration tested (one-way ANOVA followed by Newman-Keuls test; $[F_{(9,30)} = 5.667, p < 0.0001]$). As N,N-dimethyl-MTA is a potent 5-HT-releasing agent [20], this action might be contributing to the dopaminergic effects observed. Consequently, we assessed the effect of N,N-dimethyl-MTA (1 mM) upon DA levels in the presence of citalopram (a selective SERT blocker). As shown, the presence of citalopram in the perfusion fluid did not modify the N,N-dimethyl-MTA-induced increase in LS DA $\{[F_{(9,30)} = 15.70, p < 0.0001]\}$ (n = 4 for each condition; ***p < 0.001).

Locomotor activity.

Figure 3 shows the effect of acute administration of *N*,*N*-dimethyl-MTA on locomotor activity in rats. The systemic administration of this drug (2.5 or 5.0 mg/kg i.p.) produced a statistically significant increase in cumulative locomotor activity (26.6 ± 2.3 for 2.5 and 39.2 ± 1.9 for 5.0 mg/kg i.p. in horizontal cross-over) compared with saline administration (11.0 ± 1.1 horizontal cross-over).

Aortic contraction.

Figure 4 shows concentration–response curves to phenylephrine, MTA and *N*,*N*-dimethyl-MTA in the test of aortic contraction *in vitro*. Phenylephrine, a selective α_1 -adrenergic receptor agonist, induced a strong contraction with a halfmaximal effective concentration (EC₅₀) of 8.87 × 10⁻⁸ M. Instead, the EC₅₀ for MTA was 2.84 × 10⁻⁵ M, whereas *N*,*N*-dimethyl-MTA was inactive in this test.

Discussion

Several neuropathologies are associated with DA deficiency. In this sense, Parkinson's disease and ADHD are treated pharmacologically with dopaminergic agonists [29] and amphetamine analogues [30], respectively. In other pathologies such as obesity, amphetamine and amphetamine-type stimulants (e.g. fenfluramine, dexfenfluramine, phentermine, diethylpropion, mazindol, phenylpropanolamine) have been widely used [31]. However, pre-clinical and clinical evidence shows that



Fig. 2. Effects of *N*,*N*-dimethyl-methylthioamphetamine (MTA) on extracellular dopamine levels in the lateral septum. Drugs were administered through the microdialysis probe. The grey bar indicates the time during which *N*,*N*-dimethyl-MTA was perfused (n = 4 for each condition). Asterisks indicate a significant difference (***p < 0.001) when comparing the effect of *N*,*N*-dimethyl-MTA with the respective basal levels (one-way ANOVA followed by the Newman–Keuls multiple comparison test).

these drugs can produce some serious cardiovascular reactions as potential cardiac valve problems [32,33], haemorrhagic stroke [34–36] and aortic contraction [37,38]. In this context, the development of novel amphetamine derivatives with a better safety profile (i.e. no cardiovascular toxicity) may be a good alternative to find potential pharmacological tools for the treatment for ADHD, obesity, narcolepsy and as replacement therapy for psychostimulant addiction [39,40].

In the present study, we demonstrate that, similarly to other amphetamine derivatives like MTA, N,N-dimethyl-MTA was able to produce dopaminergic effects. However, this drug did not produce any effect on aortic contraction. Our results show that N,N-dimethyl-MTA increases the extracellular levels of DA in the rat LS in a concentration-dependent manner. N,N-dimethyl-MTA was less potent than MTA in this assay, which is similar to that observed when assessing the effects of both drugs upon 5-HT [20]. In addition, N,N-dimethyl-MTAinduced increase in DA was not significantly affected by the concomitant perfusion of the 5-HT uptake blocker citalopram. Nevertheless, it should be noted that in the presence of the SERT blocker, DA levels were not identical to those obtained after the perfusion of N,N-dimethyl-MTA alone, and a trend to a reduced effect was observed. This suggests that a serotonergic influence on the effects of N,N-dimethyl-MTA upon DA cannot be completely discarded. Despite this consideration, the lack of significant effect of citalopram indicates that the dopaminergic effect of N,N-dimethyl-MTA is largely independent of its actions on 5-HT transporter and suggests that it might be mediated by a direct interaction with DA transporter. However, further experiments are necessary to test this hypothesis.

On the other hand, *N*,*N*-dimethyl-MTA produces a significant dose-dependent increase in locomotor activity. Again, the



Fig. 3. Effect of *N*,*N*-dimethyl-methylthioamphetamine (MTA) (2.5 or 5.0 mg/kg i.p.; n = 5 for each dose) on locomotor activity. Saline control rats were n = 5. Asterisks indicate a significant difference (***p < 0.001) when comparing the effect of *N*,*N*-dimethyl-MTA with saline administration or between doses (one-way ANOVA followed by the Newman–Keuls multiple comparison test).



Fig. 4. Contraction of rat aortic rings by phenylephrine, methylthioamphetamine (MTA) and N,N-dimethyl-MTA. Data are the mean \pm S.E.M. of four experiments, each performed in duplicate.

effect produced by *N*,*N*-dimethyl-MTA was slightly less potent than that produced by MTA under identical conditions [19]. Thus, even though *N*,*N*-dimethyl-MTA was less potent than MTA both, at neurochemical and behavioural levels, it still generated significant effects at a relevant concentrations/ doses and showed the same profile previously observed for MTA [see 19]. On the other hand, a striking difference between both drugs was observed in regard to their effects on rat aortic contraction. Thus, while MTA (and the reference drug phenylephrine) caused a concentration-dependent contraction of the aorta, *N*,*N*-dimethyl-MTA was completely devoid of effect at concentrations up to 1 mM. It should be noted that both the EC_{50} and the E_{max} determined here for MTA are very similar to those previously reported using an almost identical protocol [16].

It has been shown that the aortic contraction produced by MTA is mediated by the noradrenaline transporter (NET), as pre-treatment with nisoxetine (a NET blocker) prevents this effect [16]. It is tempting to speculate that the lack of effect observed for N,N-dimethyl-MTA on the aortic contraction assay may be related to a decrease in the affinity of this drug for NET as compared with MTA, due to the presence of the tertiary amine function. Accordingly, it has been previously shown that N-substitution leads to a decrease in NET affinity for several different amphetamine derivatives [1,41-43]. In this sense, data not shown in this study indicate that different substituents at the para position of the benzene ring in the MTA molecule do not affect aortic contraction, while the replacement of a hydrogen on the amino group of the MTA molecule by an allyl group decreases the potency in this assay. Nevertheless, further experiments are necessary to evaluate this hypothesis. In addition, as with other amphetamine derivatives [44], the presence of the two methyl groups in the N,N-dimethyl-MTA molecule should increase its brain penetration as compared with MTA. Therefore, N-substitution might be important for the design of novel amphetamine derivatives from both, pharmacodynamic and pharmacokinetic points of view.

Conclusion

N,*N*-Dimethyl-MTA is a drug that increases extracellular dopamine levels and has no effect on rat aortic contraction. This drug might be a valuable lead for the development of novel pharmacological tools with an improved cardiovascular safety profile, aimed to the treatment for chronic diseases such as obesity or neurobehavioural disorders like ADHD. Subsequent *in vivo* studies will be conducted to test these effects. The effect of *N*,*N*-disubstitution of amphetamine derivatives as a mean to modulate their affinity for different monoamine transporters deserves further study.

Conflicts of interest and source of funding

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