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An antisense oligonucleotide targeted at MAO-B attenuates rat striatal serotonergic neurotoxicity induced by MDMA

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Abstract

The present study was designed to elucidate the role of dopamine (DA) metabolism in the serotonergic neurotoxicity induced by 3,4-methylenedioxymethamphetamine (MDMA). An antisense (AS) oligonucleotide (ODN) sequence targeted at monoamine oxidase-B (MAO-B) was utilized to attenuate MAO-B activity prior to MDMA administration. Sprague–Dawley rats were surgically implanted with intracerebroventricular (icv) cannulae and received a continuous infusion of MAO-B AS-ODN via an osmotic minipump. Constant AS ODN infusion for 7 days at a rate of 0.5 μl/h (total daily dose 600 pmol) resulted in a 63% knockdown of MAO-B activity. MDMA (40 mg/kg, sc) produced a rise in body temperature within 1 h of MDMA administration and a reduction in striatal serotonin (5-HT) and 5-hydroxyindole acetic acid (5-HIAA) levels 7 days later. Pretreatment with the MAO-B AS ODN prior to MDMA attenuated this reduction in serotonergic markers, yet had no effect on MDMA-induced hyperthermia. Furthermore, in vivo microdialysis revealed that previous AS ODN treatment failed to alter the acute DA release induced by MDMA (10 mg/kg, sc) within the striatum. These results indicate that MAO-B plays an integral role in the development of MDMA-induced neurotoxicity while not affecting MDMA-induced hyperthermia or acute DA release.

Keywords: Antisense; MAO-B; MDMA; Dopamine; Serotonergic neurotoxicity; Microdialysis

1. Introduction

With the increasing abuse of the street drug "Ecstasy" [3,4-methylenedioxymethamphetamine (MDMA)], possible long-term neurotoxic effects of the drug are becoming more apparent. In fact, recent positron emission tomography (PET) scan-imaging studies have indicated that chronic MDMA use in humans may lead to the selective loss of serotonergic axons (McCann et al., 1998). Multiple doses or a single high dose of MDMA also induce serotonergic neurotoxicity in a variety of animal models as well as non-human primates (for a review, see Sprague et al., 1998). Although the biochemical events occurring in the development of the neurotoxicity have been well documented, the precise mechanisms and sequence of events involved have yet to be elucidated.

Numerous studies have suggested that dopamine (DA) plays a critical role as the neurotoxin or penultimate toxin in the serotonergic neurotoxicity induced by MDMA. Evidence in support of DA involvement includes the finding that administration of the DA precursor, L-DOPA, prior to MDMA results in potentiation of the neurotoxic effect (Schmidt et al., 1990). Furthermore, a linear correlation exists between extracellular DA concentration and the extent of long-term serotonergic toxicity (Nash and Nichols, 1991). Treatment with α-methyl-*p*-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, prior to administration of MDMA protects against serotonin (5-HT) terminal loss (Stone et al., 1988), as does administration of ketanserin, which indirectly prevents enhanced DA synthesis and release (Nash, 1990). Additionally, if dopaminergic projections are destroyed with 6-hydroxydopamine, the neurotoxicity is attenuated (Schmidt et al., 1990). Likewise, rat pups less than 28 days old with undeveloped dopaminergic systems do not exhibit MDMA-induced neurotoxicity. At 35 days, however, the dopaminergic system is developed and the neurotoxicity occurs (Aguirre et al., 1998). Whereas MDMA itself induces

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DA release, the acute increase in postsynaptic 5-HT that occurs concomitantly markedly amplifies the concentration of extracellular DA (Gudelsky and Nash, 1996). The dramatically elevated acute DA levels share an inverse relationship with the long-term 5-HT depletion that also occurs (Nash and Nichols, 1991).

We have proposed that excessive extracellular DA may be taken up into the depleted 5-HT terminals (Sprague et al., 1998). This hypothesis is consistent with the observation that the 5-HT uptake carrier will also transport DA (Faraj et al., 1994). Furthermore, selective 5-HT uptake blockers such as fluoxetine have been shown to inhibit DA uptake (Faraj et al., 1994; Sprague and Nichols, 1995) and lead to neuroprotection, even if given up to 6 h after MDMA administration (Schmidt, 1987). One proposed theory (Sprague and Nichols, 1995) suggests that the extraneous DA that has now entered the depleted 5-HT terminal could subsequently be metabolized by monoamine oxidase-B (MAO-B) within the terminal (Levitt et al., 1982). Deamination of DA by MAO-B would produce hydrogen peroxide (H_2O_2) and other free radicals leading to general oxidative stress (Cadet and Brannock, 1998) and selective damage to the 5-HT terminal. Large amounts of intracellular DA to be deaminated could lead to the generation of concentrations of reactive oxidizing species sufficient to overwhelm the protective reductive capabilities within the terminal.

The present study was designed to delineate further the role of DA metabolism in MDMA-induced serotonergic neurotoxicity by decreasing MAO-B protein expression with an antisense (AS) oligonucleotide (ODN). An explanation of the biochemical events involved in the neurotoxicity induced by MDMA will not only answer questions related to human abuse of this drug, but may also lead to new insights into brain degenerative processes.

2. Materials and methods

The present study was carried out in accordance with protocols approved by the Ohio Northern University Animal Care and Use Committee.

2.1. Animals

Adult, male, Sprague–Dawley (SD) rats (Harlan Sprague–Dawley, Indianapolis) weighing 160–190 g were used. All animals were individually housed and given ad libitum access to food and drinking water. Housing conditions were maintained at a constant temperature of 23 °C and a 12:12-h light–dark cycle.

2.2. Drugs and chemicals

The ODN sequences were obtained from Sigma-Genosys Biotechnologies (The Woodlands, TX). All other reagents were purchased from Sigma (St. Louis, MO). (±)-MDMA hydrochloride was synthesized in our laboratory (DEN) using standard methods and was 99+% pure by HPLC.

2.3. Surgical implantation of intracerebroventricular (ICV) cannulae and microdialysis probes

Rats were anesthetized with ketamine (90 mg/kg, ip) and xylazine (10 mg/kg, ip) and the ICV guide cannula (Plastics One, Roanoke, VA) was stereotaxically placed into the lateral ventricle (A—0.5, L—1.5, V—3.5 from bregma; Paxinos and Watson, 1998). The microdialysis guide cannula (CMA, Acton, MA) was stereotaxically placed into the caudate putamen (A—0.5, L—3.0, V—5.0 from bregma; Paxinos and Watson, 1998). The cannula was then fixed in place with dental acrylic supported by stainless steel screws threaded into the skull and glued into place. The animals were then given a 24-h recovery period before experimental procedures were begun.

For microdialysis, the animals were placed in a Raturn® (BAS, Lafayette, IN). The dialysis probe was connected to a Bee Hive® microinfusion pump (BAS) calibrated to deliver artificial cerebrospinal fluid (aCSF) at a rate of 1.5 μl/min. The probe was perfused for 30 min to allow for equilibration. Three baseline samples were then collected before the animals were treated with saline (sc). MDMA (10 mg/kg, sc) was given 30 min following the saline treatment. Samples were collected every 20 min for a total of 180 min posttreatment.

2.4. AS ODN and drug administration

An 18 nucleotide AS ODN sequence (5′-GCC AAA CTT TTG CAT GAC-3′) was selected from rat MAO-B cDNA (accession # M23601) corresponding to bases #121 to 138 (bases 57–75 in the mRNA coding sequence). The sequence was searched against the GenBank rodent database to insure gene specificity (or lack thereof) and to eliminate effects on other mRNAs. The pharmacodynamic effects (including acute biochemical effects) of this AS ODN, a scrambled sequence and the reverse sequence have been previously described (Sprague et al., 2001). The AS ODN sequence was suspended in a Dulbecco's phosphate-buffered saline medium containing 138 mM NaCl, 2.7 mM KCl, 0.5 mM $MgCl_2$, 1.5 mM KH_2PO_4 and 1.2 mM $CaCl_2$. The final concentration of the sequence was 50 μM. Delivery of the AS ODN was accomplished via Alzet® osmotic minipumps, which administered the AS ODN continually for seven days at a rate of 0.5 μl/h yielding a total dose of 600 pmol/day.

When examining serotonergic neurotoxicity, MDMA (40 mg/kg, sc) or saline was given after the seventh day of AS administration. Rats were sacrificed by decapitation seven days later for assessment of serotonergic deficits as an indicator of chronic toxicity. The brains were rapidly removed and the striatum was dissected out on ice. The tissue was immediately assayed for monoamines.

2.5. Measurement of biogenic amine levels

A modified procedure of Chapin et al. (1994) was used to determine neurotransmitter levels in the striatum. The aqueous portion of the mobile phase consisted of 0.05 M sodium phosphate, 0.03 M citric acid, 0.1 mM disodium ethylenediamine tetraacetate (EDTA) and 0.042% sodium octyl sulfate (SOS) dissolved in HPLC grade water. The pH of the aqueous portion of the mobile phase was in the range 2.7–2.9. The mobile phase consisted of 80% aqueous phase and 20% methanol. A Waters HPLC (Model 600) with electrochemical detection (Waters 464) and a C_{18} reverse phase analytical column (4-μm spheres; 3.9×300 mm; Waters) was used. The electrode was set at +750 mV and the flow rate was set at 0.7 ml/min.

Tissue for analysis was placed into a microcentrifuge tube and was homogenized for fifteen seconds in 500 μl of the aqueous portion of the mobile phase containing 0.1 M $HClO_4$ using a Fisher Scientific Sonic Desmembranator on a setting of four. The homogenate was then centrifuged for 6 min at $14{,}000 \times g$ at 4 °C. The supernatant (50 μl) was injected into the HPLC column. Millennium® software was used to integrate and analyze the raw data for the determination of 5-HT, 5-HIAA, DA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels.

2.6. Measurement of MAO-B activity

A modified version of our previous method (Sprague et al., 2001) was used to assess MAO-B activity. On the seventh day of AS ODN administration, striatal tissues from four animals were pooled together from the control and AS ODN treated groups. Tissue was prepared as previously described for this enzyme assay (Reyes-Parada et al., 1994). The tissue was incubated at 37 °C for 30 min in a mixture containing 1 μg/μl of the selective MAO-B substrate, 4-dimethylaminophenethylamine (DMAPEA), 1.6 units of aldehyde dehydrogenase (ADH) and 1.2 μmol of β-nicotinamide-adenine dinucleotide suspended in 0.1 M phosphate buffer (pH = 7.4). This mixture was then centrifuged at ($15{,}000 \times g$) for 10 min at 4 °C. The sample levels of DMAPEA and its metabolite 4-dimethylaminophenylacetic acid (DMAPAA) were measured via HPLC-EC detection.

2.7. Measurement of body temperature

A digital thermometer was inserted rectally to a depth of 2 cm in order to measure body temperature. Room temperature at time of analysis was 23 °C. Temperatures were measured 0, 1, 2, 3 and 4 h after administration of MDMA (40 mg/kg, sc).

2.8. Statistics

For ease of comparison, the results are presented as the means ± S.E.M. of the tissue contents of the treatment groups expressed as a percentage of corresponding saline-injected controls. Rectal temperature statistical significance was determined using an ANOVA followed by a Student–Newman–Keuls post hoc test. For in vivo microdialysis, the effects of MDMA treatment alone on DA and DOPAC levels were compared with the AS/MDMA treatment results using Student's t test ($P < .05$) at each individual time point. Each treatment group was then compared to basal DA and DOPAC levels using ANOVA. If a significant P value was obtained, a Dunnett's post hoc analysis test was subsequently performed. Biochemical measures of serotonergic neurotoxicity were assessed for significance with a paired t test.

3. Results

3.1. Effect of the AS ODN on MAO-B activity

We had previously reported that this AS ODN given twice daily for 3.5 days (200 pmol/day) reduced MAO-B activity by 40% (Sprague et al., 2001). Utilizing continuous minipump administration over 7 days enhanced the knockdown to 63% of control.

3.2. Effect of the AS ODN on MDMA-induced hyperthermia

There was no significant difference in the basal temperatures between groups. The animals treated with MDMA alone exhibited a nonsignificant increase in body temperature when compared to the saline treated group. The animals treated with the AS ODN experienced a significant rise in body temperature ($P < .01$) after MDMA. The temperatures of the MDMA and AS/MDMA treatment groups were not significantly different from each other, with the

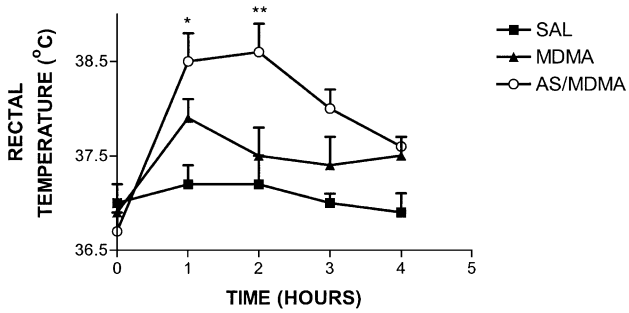

Fig. 1. Rectal temperatures in MDMA-treated rats that previously received ICV infusion of AS-ODN directed at MAO-B. AS-ODN (600 pmol/day) was infused into the ventricle by an osmotic minipump for 7 days prior to MDMA (40 mg/kg, sc) treatment. Results shown are means ± S.E.M., $n = 6$. There was no significant difference in the basal temperatures between groups. The group treated with MDMA alone exhibited a rise in body temperature when compared to the saline-treated group. The MDMA and AS/MDMA treatment groups were not significantly different with the exception of the 2-h time point. * Significantly different from saline ($P < .01$). ** Significantly different from all other groups ($P < .05$).

exception of the 2-h time point, where the AS/MDMA treatment resulted in a significantly higher temperature (Fig. 1).

3.3. Effect of AS ODN on the MDMA-induced extracellular DA increase

MDMA treatment resulted in increased (P=.05) extracellular DA 40, 60 and 80 min after treatment. The AS/MDMA treatment also gave an increased DA release that did not differ from MDMA treatment alone (Fig. 2A). The saline injection did not produce a significant change in the acute DA level in either group. Previous results from our laboratory have shown that a saline injection does not significantly alter DA release over a 180-minute period (Data not shown). MDMA led to a significant increase in DA turnover as reflected by an increase in DOPAC levels 40 min after treatment. AS ODN treatment predictably blocked this elevation in DA turnover (Fig. 2B).

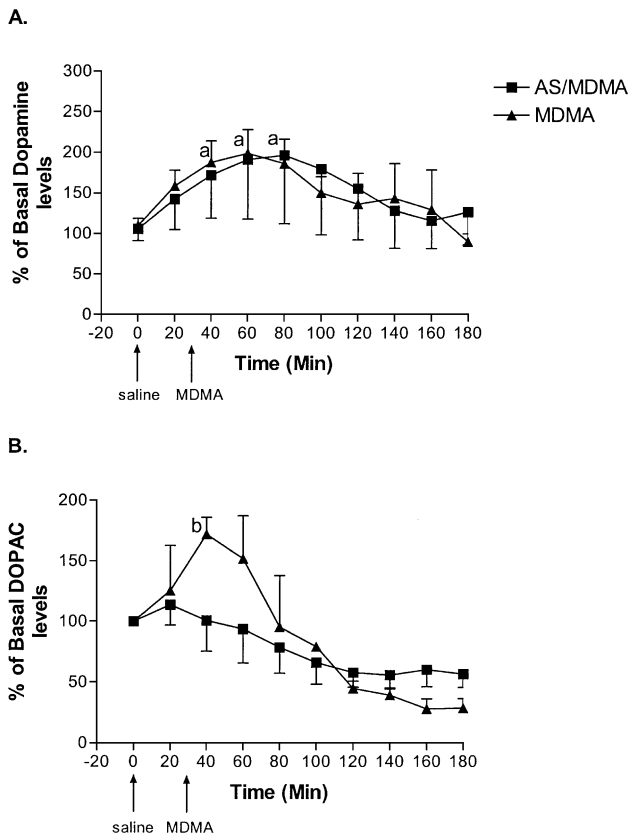

Fig. 2. (A) Effects of MDMA (10 mg/kg, sc) on dialysate DA in the striatum. (B) Effects of MDMA (10 mg/kg, sc) on dialysate DOPAC in the striatum. Results are means ± S.E.M. (n=3–4) of the amount of DA and DOPAC found in 20-min dialysate samples expressed as percent of basal values. All saline injections were given at time zero and MDMA injections were given 30 min after saline. [a]DA after MDMA is significantly different from baseline levels. [b]Significant difference between groups at each time point.

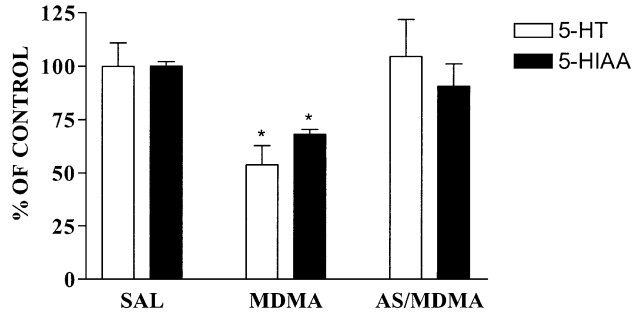

Fig. 3. The MDMA-induced neurotoxic response after 7 days of treatment with MAO-B AS-ODN. Animals were given constant unilateral infusion of MAO-B AS-ODN (600 pmol/day) for 7 days. On Day 8, animals were administered a single injection of MDMA (40 mg/kg, sc). One week following MDMA administration, rats were sacrificed and the striatum from the infused side was analyzed to determine the degree of MDMA-induced 5-HT neuronal loss. Saline control values were 5-HT 282 ± 31 and 5-HIAA 416.8 ± 20 pg/mg wet weight. Each value is the mean ± S.E.M for n=5–6 animals. * Significant difference between control and MDMA treatment groups (P<.05). Comparison of MDMA to the AS/MDMA groups yielded a P value of .058.

3.4. Effect of AS ODN on MDMA-induced serotonergic neurotoxicity

MDMA treatment resulted in a 46% reduction in 5-HT and a 32% reduction in 5-HIAA in the striatum seven days after drug administration. Animals treated continuously for seven days with the MAO-B AS ODN (600 pmol/day) showed protection from this reduction in serotonergic markers. Animals receiving the AS ODN sequence in combination with MDMA had 5-HT and 5-HIAA levels of 104% and 91% of control, respectively. Thus, AS ODN targeting MAO-B blocked the reduction in 5-HT and 5-HIAA levels produced by MDMA alone (Fig. 3).

4. Discussion

In order to examine the role of DA metabolism in the serotonergic neurotoxicity of MDMA, it was necessary to reduce the activity of MAO-B. Our decision to utilize an AS ODN as a means to knockdown protein expression was based on work that revealed that many of the pharmacological agents used in CNS research to decrease MAO-B activity also possess confounding, peripheral pharmacological effects. For example, the MAO-B inhibitors, L-deprenyl and MDL-72974, have been shown to possess free radical scavenging activity (Knoll, 1988; Thomas et al., 1994). Further contributions to the overall pharmacological and neuroprotective effects of L-deprenyl include the ability of this agent to inhibit amine uptake (Knoll, 1987) and to induce the expression of nerve growth factor (Semkova et al., 1996). AS ODN technologies, however, can successfully decrease MAO-B activity without introducing ancillary neuroprotective effects.

Numerous studies continue to support the hypothesis of a role for DA metabolism by MAO-B in the development of MDMA-induced serotonergic neurotoxicity. For instance, MAO-B knockout mice were shown not to be susceptible to MDMA-induced serotonergic damage (Fornai et al., 2001). Mazindol, a DA transporter (DAT) inhibitor, prevents both increases in DA levels following treatment with MDMA and serotonergic neurotoxicity (Shankaran et al., 1999). Further, using AS ODN technology, Kanthasamy and Nichols (submitted for publication) found that osmotic minipump administration of an AS ODN targeted against the DAT led to a 70% reduction in DAT levels and also afforded protection from MDMA-induced neurotoxicity.

The results of the present study confirm the utility of osmotic minipump administration of AS ODN. The data show that prolonged infusion with MAO-B AS ODN can block the striatal 5-HT and 5-HIAA deficits induced by MDMA treatment (Fig. 3) without altering acute MDMA-induced DA release (Fig. 2). Previous work in this laboratory showed that dosing with the MAO-B AS ODN twice daily for 3.5 days led only to a 40% knockdown of MAO-B activity and did not attenuate the subsequent MDMA-induced neurotoxicity (Sprague et al., 1999). Conversely, AS ODN delivery via continuous infusion for 7 days led to a 63% knockdown of MAO-B activity, which did result in neuroprotection. These results appear to confirm the involvement of MAO-B in the MDMA neurotoxicity process and demonstrate that there is a threshold level of MAO-B reduction (i.e. $>40\%$) necessary to afford neuroprotection.

Despite extensive evidence supporting a role for the dopaminergic system in MDMA neurotoxicity, some investigators argue that hyperthermia is the key player in the process. For example, Malberg et al. (1996) showed that the neuroprotective effect of ketanserin was lost upon elevation of body temperature. They also reported that pretreatment of animals with AMPT induced a hypothermia and afforded neuroprotection, whereas warming these animals resulted in a loss of the protection from serotonergic toxicity (it should be noted, however, that in the same study it was found that fluoxetine did not block MDMA-induced hyperthermia, yet still afforded protection against serotonergic neurotoxicity). Similarly, Colado et al. (1998, 1999a,b) have suggested that part of the neuroprotection seen with haloperidol and the potentiation of toxicity seen with L-DOPA might have resulted from manipulation of MDMA-induced hyperthermia instead of direct effects on the dopaminergic system. In studying the effects of L-DOPA on MDMA-induced free radical production, however, these researchers examined only the hippocampus, where there is little to no dopaminergic innervation, rather than a DA rich region such as the striatum. Therefore, it is not surprising that L-DOPA did not result in a dramatic increase in MDMA-induced free radical production in that brain region. Indeed, Shankaran and Gudelsky (1998) have suggested that the neurotoxic events in the hippocampus must be mediated by some mechanism other than DA metabolism.

Clearly, effects on body temperature confound interpretation of many of the pharmacological studies of MDMA neurotoxicity. Many agents that modulate the neurochemical effects of MDMA, providing neuroprotection, also antagonize the hyperthermic response elicited by MDMA. It is our hypothesis that increased body temperature can potentiate neurotoxic events, but that the underlying basis of MDMA-induced neurotoxicity is unrelated to the production of hyperthermia. It is well recognized that a reduction in body temperature can slow chemical reactions induced by a variety of insults that lead to neurotoxicity (Bowyer et al., 1993).

Recently, Yuan et al. (2001) reported that depletion of vesicular stores of DA with reserpine 18-h before MDMA failed to attenuate the neurotoxicity of MDMA. These authors interpret their results to suggest that DA may not play a crucial role in the serotonergic neurotoxicity of MDMA. Reserpine-induced monoamine depletion, however, leads to a block not only of acute DA release but also the acute release of 5-HT induced by MDMA (Sabol and Seiden, 1998) and would also be expected to block MDMA-induced NE release. The neurochemical profile involved in the neurotoxic process is altered in so many ways by reserpine pretreatment that any attempt to conclude that it affects a specific role of DA in the neurotoxic process can only be considered speculative. Indeed, in other studies, reserpine did afford protection against MDMA-induced neurotoxicity (Schmidt et al., 1990). This type of confound is exactly why the precise pharmacological specificity of an AS ODN can be so powerful.

In summary, AS ODN treatment led to attenuation of serotonergic toxicity but failed to prevent the hyperthermia elicited by MDMA (Fig. 1) and did not alter the acute affects of MDMA on DA release (Fig. 2). These results provide further support for the role of DA as a functionally important component of the neurotoxic process, at least in the striatum, rather than serving simply as a correlative indicator for hyperthermia or some other process that is the ultimate necessary event for toxicity development.

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