European Journal of Pharmacology, 218 (1992) 287–293

EJP 52554

Response of monoaminergic and neuropeptide systems to 4-methylaminorex: a new stimulant of abuse

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Received 13 February 1992, revised MS received 24 April 1992, accepted 5 May 1992

4-Methylaminorex is an amphetamine analog which has recently gained attention due to its potential as a stimulant of abuse and the ease with which it is synthesized. Administration of acute and multiple doses of 4-methylaminorex caused rapid (3-h) and long-term (7-day) declines in striatal tryptophan hydroxylase activity with few changes in other serotonergic parameters. The acute response by tryptophan hydroxylase to this drug was reversed by incubating the tissues in a reducing environment suggesting that 4-methylaminorex alters this enzyme through oxidative mechanisms. The 4-methylaminorex-induced long-term reduction in tryptophan hydroxylase activity might be due to neurotoxic action on serotonergic systems. In contrast, although a decline in striatal tyrosine hydroxylase occurred 3 h following a single dose of 4-methylaminorex, no changes in this enzyme were observed at 7 days after acute or multiple dosing with this drug. This result suggests that 4-methylaminorex is not neurotoxic to the dopaminergic neurons. Even though this amphetamine analog apparently does not have long-term effects on dopaminergic systems, it does appear to enhance substantially dopaminergic activity. Evidence for increased dopamine activity resulting from 4-methylaminorex administration included dramatic but temporary rises in the levels of nigral neurotensin, dynorphin A and substance P following multiple drug administration. Similar peptide changes have been observed with other amphetamine-related stimulants and are mediated by increases in dopaminergic activity. In summary, 4-methylaminorex has significant impact on monoaminergic pathways. In general, its spectrum of effects on these systems is like that of the ring-substituted amphetamines, such as methylenedioxymethamphetamine.

Amphetamines; Basal ganglia; Dopamine; Drug abuse; Dynorphin A; 4-Methylaminorex; Neurotensin; 5-HT (5-hydroxytryptamine, serotonin); Substance P; Tryptophan hydroxylase

1. Introduction

Several analogs of amphetamine currently are being synthesized by clandestine laboratories for illicit marketing. These amphetamine derivatives, for the most part, retain amphetamine-like abuse liability as well as varying effects on locomotor and stereotypic activity. Besides their immediate effects on behavior, some of these amphetamine analogs are neurotoxic causing long-term damage in either or both central nervous system (CNS) dopaminergic and serotonergic neurons (Hotchkiss and Gibb, 1980; Ricaurte et al., 1985; Schmidt et al., 1985; Stone et al., 1987; Wagner et al., 1980; Wilson et al., 1989).

4-Methylaminorex (2-amino-4-methyl-5-phenyl-2-oxazolamine), one of the most recent of these illegally manufactured amphetamines to appear on the streets, has been confiscated by authorities in Florida, California and Pennsylvania (Drug Control Section, 1988; Davis and Brewster, 1987). This agent differs from the ring-substituted amphetamine analogs, such as methylenedioxymethamphetamine (MDMA), as it belongs to the oxazoline chemical class and has a side chain substitution much like pemoline, a Schedule IV CNS stimulant (fig. 1). 4-Methylaminorex was originally described in 1963 as an indirect-acting sympathomimetic drug with anorectic properties (Poos et al., 1963; Roszkowski and Kelly, 1963; Yelnesky and Katz, 1963).

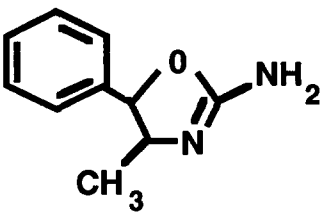

Fig. 1. Molecular structure of 4-methylaminorex.

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The cis-(+)isomer is easily synthesized in a one-step reaction from the condensation of phenylpropanolamine with cyanogen bromide. If norpseudoephedrine is substituted for the phenylpropanolamine, the trans isomer is formed (Poos et al., 1963). Even though both the cis and trans isomers are thought to have similar stimulant and anorectic properties comparable to amphetamine (Roszkowski and Kelly, 1963: Yelnosky and Katz, 1963), only the cis isomer of 4-methylaminorex was classified as a Schedule I substance in April of 1989.

As a drug of abuse, 4-methylaminorex has been referred to by various 'street names' including, U4EA, EU4EA or U4Euh and has been masqueraded by drug dealers as methamphetamine or cocaine (Drug Control Section, 1988). In fact, users have described the effects of 4-methylaminorex to be similar to these commonly abused stimulants; thus, it is not surprising that in preliminary studies, 4-methylaminorex was self-administered by monkeys in a manner similar to cocaine (Drug Control Section, 1988).

The scheduling of 4-methylaminorex underscores the concern of authorities that the accessibility of precursors and the ease of synthesis will lead to increased abuse of this drug. Even so, very little is known about the pharmacology and toxicology of this agent. A recent report by Bunker et al. (1990) demonstrated that after a single administration, 4-methylaminorex increases dopamine (DA) release causing a dramatic rise in the striatal DA metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid. In addition, a dose-dependent decline in the tryptophan hydroxylase (TPH) activity of striatum, frontal cortex and hippocampus occurs 3 h after a single injection of this drug. The objective of the present study was to elucidate further the neurochemical effects of this stimulant and identify the mechanisms of action which account for the changes observed following 4-methylaminorex treatment.

2. Materials and methods

Male Sprague Dawley rats (150–220 g) were housed in a temperature-controlled room (22°C) with a 12-h alternating light–dark cycle. They were allowed free access to standard laboratory food and water.

2.1. Treatment and dissection

The (±)-cis-4-methylaminorex (supplied by the National Institute on Drug Abuse) was dissolved in 0.9% saline and administered subcutaneously as either a single or multiple (five doses with a 6-h interval between doses) administrations. Animals were decapitated 3 h, 18 h or 7 days after treatment and corresponding control groups were identically treated with saline alone. Because the duration of action of 4-methylaminorex (i.e., increased locomotor activity) was similar to that observed with a comparable dose of other amphetamine analogs, we used the same dosing protocols we have previously employed for the study of methamphetamine (Hotchkiss and Gibb, 1980). Immediately following sacrificing, the brain was rapidly removed and placed on ice, and the neostriata (including the caudate nucleus and globus pallidus) were removed bilaterally. For one experiment (see fig. 4), the frontal cortex was also removed from the 3-h group. The remaining tissue was frozen on dry ice and the substantia nigra was dissected from 1-mm-thick sections of the mesencephalon according to the Atlas of Konig and Klippel (1963). All samples were stored at −80°C until assayed.

2.2. Enzyme assays

One of the paired-striata was weighed and homogenized in 80–200 μl of 50 mM HEPES buffer (Sigma Chemical Co., St. Louis, MO) (pH 7.4), containing 0.2% Triton X-100 (v/v) and 5 mM dithiothreitol (Cal-biochem-Behring Corp., San Diego, CA). After centrifugation at 27000 × *g* for 15 min, duplicate 7.5-μl aliquots of the supernatant were removed and assayed for tryptophan hydroxylase (TPH) activity by a modified $^{14}CO_2$-trapping procedure ([^{14}C]tryptophan: New England Nuclear, Boston, MA) (Ichiyama et al., 1970; Sitaram and Lees, 1978) as described by Hotchkiss et al. (1979). In some cases, identical 10-μl aliquots were diluted to 50 μl with glass-distilled water and analyzed for activity of tyrosine hydroxylase according to the method of Nagatsu et al. (1964) by measuring the formation of ^3H_2O. [^{3}H]Tyrosine and ^3H_2O were separated according to the method of Reinhard et al. (1986). The incubation medium in each tube (100 μl total volume) contained 200000 cpm of L-[3,5-^{3}H]-tyrosine (54.2 Ci/mmol, New England Nuclear, Boston, MA), 10 nmol tyrosine, 100 nmol ferrous ammonium sulfate, 320 nmol dl-6-methyl-5,6,7,8-tetrahydrobiopterin (Sigma Chemical Co., St. Louis, MO), 10 nm 2-mercaptoethanol and 20 μmol sodium acetate. Potential direct interaction between 4-methylaminorex and tyrosine hydroxylase was evaluated by adding 3 mM of the drug to striata from control animals that were prepared for the enzyme analysis as described above. The presence of this high concentration of 4-methylaminorex had no significant effect on tyrosine hydroxylase activity measured under the described conditions.

2.3. Determination of monoamines and metabolites of monoamines

Neostriatal concentrations of 5-hydroxytryptamine (5-HT) and dopamine (DA) and their respective primary metabolites, 5-hydroxyindoleacetic acid (5-HIAA) and DOPAC, were measured in the contralateral tissue by high-performance liquid chromatography coupled with electrochemical detection. Tissues were homogenized in 0.5 ml mobile phase buffer (0.15 M monochloroacetic acid, 2.0 mM EDTA, 0.1 mM 1-octanesulfonic acid and 12.5% methanol; pH 2.9) and centrifuged at $4080 \times g$ for 30 min. The resulting supernatant fraction was filtered through a 0.2-μm microfilter system (Bioanalytical Systems Inc., West Lafayette, IN), and 50 μl of the filtered supernatant were injected onto a 12.5-cm Whatman PartiSphere C-18 reverse-phase column. The eluent was monitored with an amperometric electrochemical detector (model LC-4B; Bioanalytical Systems., Inc., West Lafayette, IN), with the potential set at +0.73 V. The concentrations of monoamines and their metabolites in tissue were quantified by comparison with a calibration curve, derived from standards of known concentration, prepared in mobile phase buffer.

2.4. Neuropeptide assays

Substantia nigras were homogenized in 0.3 ml of 0.01 N HCl in 12 × 75-mm silanized glass tubes with an Tissuemizer homogenizer (Tekmar, Cincinnati, OH) for 15 s, and 20 μl were removed for protein determination (Bradford, 1976). The homogenate was heated in boiling water for 10 min, after which the samples were centrifuged 30 min at $3000 \times g$, and the resulting supernatant was removed for lyophilization. Samples were reconstituted in 0.5 ml phosphate-buffered saline with 0.1% gelatin (pH 7.4). Neurotensin, dynorphin A-(1–17) and substance P concentrations were determined by radioimmunoassay as previously reported (Hanson and Lovenberg, 1980; Letter et al., 1987b; Hanson et al., 1988). The concentrations were measured as picograms of neurotensin-, dynorphin- or substance P-like immunoreactivity per milligram protein.

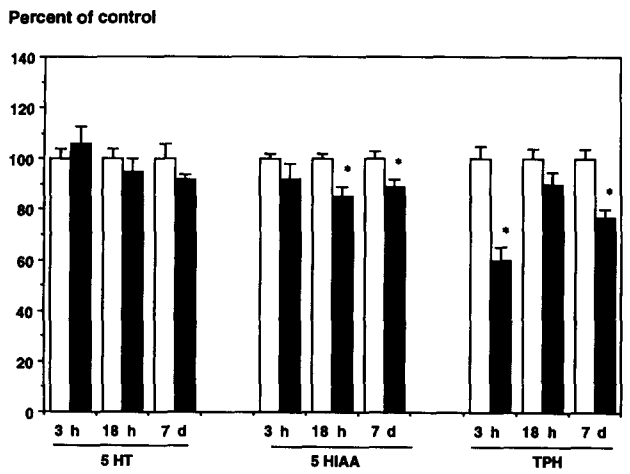

Fig. 2. Response of the striatal serotonergic system 3 h, 18 h and 7 days following a single injection of 4-methylaminorex (10 mg/kg). The ranges of the mean control concentration for 5-HT and 5-HIAA were 0.46–0.52 and 0.48–0.52 μg/g tissue, respectively. The range of the mean control activities for TPH was 17.0–19.1 nmol of hydroxylated tryptophan/h per g tissue. * $P < 0.05$ compared to the respective control. Key: □ control; ■ 4-methylaminorex.

2.5. Statistics

Data presented are the means ± S.E.M. and expressed as a percentage of corresponding saline-injected controls for ease of comparison. Each group represented four to eight animals. The data were analyzed by the two-tailed Student's t-test. Differences between groups were considered significant when the probability that they were zero was less than 5%.

3. Results

3.1. Time response of striatal 5-HT and DA systems to a single dose of 4-methylaminorex

Animals were killed 3 h, 18 h or 7 days after a single administration of 4-methylaminorex (10 mg/kg); this dose was previously shown to alter significantly serotonergic systems (Bunker et al., 1990). Higher doses (i.e., 15 mg/kg and greater) were not used as they often caused severe, and sometimes fatal, seizures. A significant reduction in striatal TPH activity after 3 h and 7 days suggests that 4-methylaminorex caused both short- and long-term effects on the serotonergic system (fig. 2): the decrease in striatal TPH activity at 3 h (fig. 2) confirmed the report of Bunker et al. (1990). In addition, striatal 5-HIAA levels were depressed 18 h and 7 days after a single 4-methylaminorex administration. A significant decline in striatal tyrosine hydroxylase activity also occurred 3 h after this treatment. No other significant changes were observed in any of the DA parameters after 3 h, 18 h or 7 days; thus, the effect of a single dose of 4-methylaminorex on the striatal DA system was short-lived (fig. 3).

3.2. Reversal of the 4-methylaminorex effects on TPH activity by a reducing environment

It was previously reported that a decline in TPH activity occurs in frontal cortex in a manner similar to that seen in the striatum 3 h after a single 4-methylaminorex administration (Bunker et al., 1990). Recent studies demonstrated that early reduction in TPH ac-

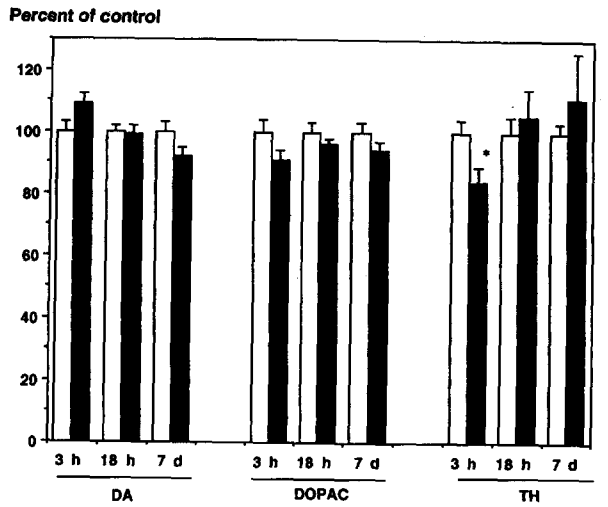

Fig. 3. Response of the striatal dopaminergic system 3 h, 18 h and 7 days following a single injection of 4-methylaminorex (10 mg/kg). The ranges of the mean control concentrations for DA and DOPAC were 7.0–9.4 and 0.88–1.22 μg/g tissue. The range of the mean control activities for tyrosine hydroxylase was 1480–1639 nmol of hydroxylated tyrosine/h per g tissue. * $P < 0.05$ compared to the respective control. Key: □ control; ■ 4-methylaminorex.

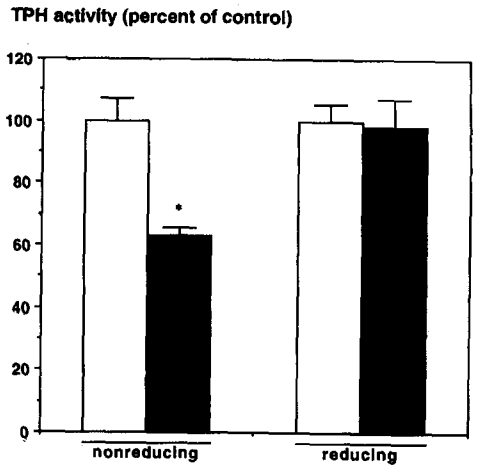

Fig. 4. Cortical TPH activity before (nonreducing) and after (reducing) a 24-h anaerobic incubation (under nitrogen gas in the presence of dithiothreitol and Fe^{2+}) from rats killed 3 h after receiving a single dose of 4-methylaminorex (10 mg/kg) or saline. Results are the means ± S.E.M. expressed as a percent of time-matched control. Control TPH activity, before and after incubation, respectively, was 59 and 77 nmol of hydroxylated tryptophan/h per g tissue. * $P < 0.05$ compared to the respective control. Key: □ control; ■ 4-methylaminorex.

tivity after treatment with amphetamine analogs is due to oxidative factors and can be reversed by in vitro incubation of tissues in a reducing environment (Stone et al., 1989). Consequently, cortical tissue was used to determine if a 24-h incubation in the presence of reducing factors would reverse the decline in TPH activity induced by a single dose of 4-methylaminorex. For this experiment cortical tissue was taken from the group of 3-h rats used for figs. 2 and 3. As observed in the striatum (fig. 2), a single 4-methylaminorex dose (10 mg/kg) decreased cortical TPH activity 38% in the frontal cortex; however, when cortical tissues from both control and 4-methylaminorex-treated animals were placed for 24 h in reducing conditions (anaerobic incubation under nitrogen gas with 5 mM dithiothreitol and 50 μM Fe^{2+}), there was no significant difference in TPH activity between 4-methylaminorex- and saline-treated animals (fig. 4).

3.3. Time response of striatal DA and 5-HT systems to multiple administrations of 4-methylaminorex

In order to compare the effects of acute and multiple administrations of 4-methylaminorex, animals were given five doses of this drug at 6-h intervals and killed 3 h, 18 h and 7 days later. The only significant changes in the striatal DA system, following multiple 4-methylaminorex administrations, were 22 and 18% increases in DA and DOPAC levels, respectively, observed 3 h after drug administration (fig. 6). A different 4-methylaminorex response occurred in the striatal 5-HT systems: multiple administrations of 4-methylaminorex significantly depressed TPH activity at 3 h, 18 h and 7 days following treatment, but had no significant effect on tissue levels of 5-HT or 5-HIAA at any of the time points evaluated (fig. 5).

3.4. Time responses of nigral neuropeptides to multiple doses of 4-methylaminorex

The response of nigral systems to 4-methylaminorex have not been previously reported. Administration of

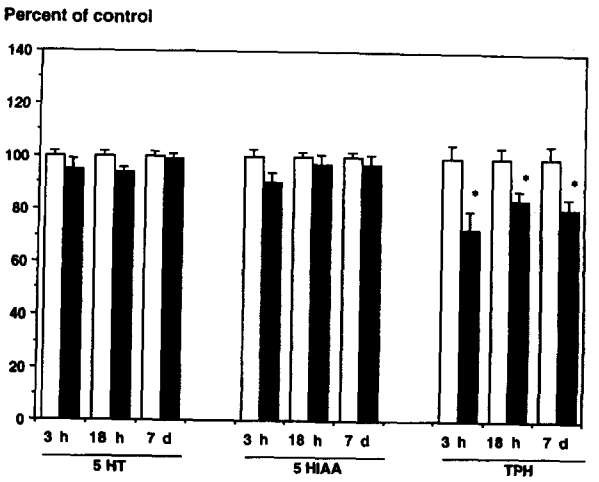

Fig. 5. Response of the striatal serotonergic system 3 h, 18 h and 7 days following multiple administrations (5 doses) of 4-methylaminorex (10 mg/kg per dose). The ranges of the mean control concentrations for 5-HT and 5-HIAA were 0.29–0.52 and 0.22–0.34 μg/g tissue, respectively. The range of the mean control activities for TPH was 21.5–39.0 nmol of hydroxylated tryptophan/h per g tissue. * $P < 0.05$ compared to the respective control. Key: □ control; ■ 4-methylaminorex.

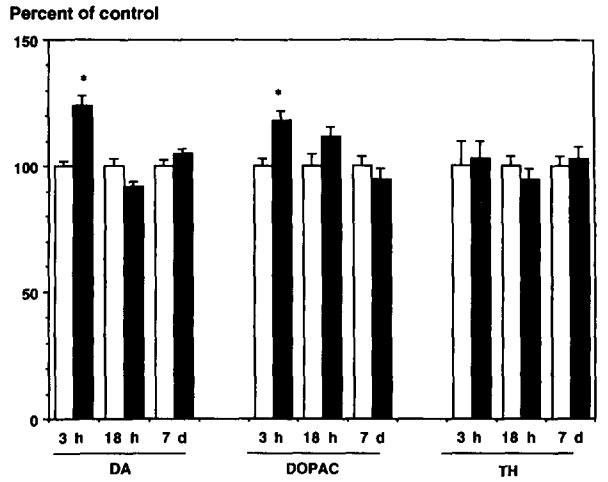

Fig. 6. Response of the striatal dopaminergic system 3 h, 18 h and 7 days following multiple injections of 4-methylaminorex (see fig. 5 for details). The ranges of the mean control concentration for DA and DOPAC were 5.0–9.1 and 0.53–0.96 $\mu g/g$ tissue, respectively. The range of the mean control activities for tyrosine hydroxylase was 1532–1588 nmol of hydroxylated tyrosine/h per g tissue. * $P < 0.05$ compared to the respective control. Key: □ control; ■ 4-methylaminorex.

some amphetamine analogs profoundly alter substance P, neurotensin and dynorphin pathways associated with the substantia nigra by increasing dopaminergic activity (Hanson and Lovenberg, 1980; Hanson et al., 1989a,b; Letter et al., 1987a,b). The response by these nigral neuropeptide projections was therefore determined 3 h, 18 h and 7 days following five doses of 4-methylaminorex. The changes in the neurotensin and dynorphin systems to this drug were similar as dramatic increases in peptide levels of approximately 400% of

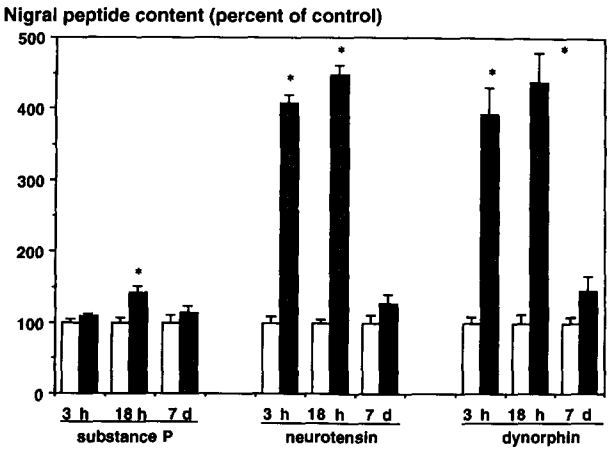

Fig. 7. Response of nigral neuropeptide systems 3 h, 18 h and 7 days following multiple injections of 4-methylaminorex (see fig. 5 for details). The ranges of the mean control concentrations for substance P, neurotensin and dynorphin were 18.3–18.7 ng/mg protein, 594–659 pg/mg protein and 317–347 pg/mg protein, respectively. * $P < 0.05$ compared to the respective controls. Key: □ control; ■ 4-methylaminorex.

control occurred 3 and 18 h after treatment: by 7 days both NTLI and DLI levels approached control levels (fig. 7). In contrast, nigral levels of substance P were significantly increased (142% of control) only 18 h after 4-methylaminorex treatment, but were not different from respective controls at either 3 h or 7 days.

4. Discussion

This study elucidates the monoaminergic effects of the relatively new stimulant of abuse, 4-methylaminorex. Of significance is the finding that both a single and multiple administrations of this drug caused an approximately 20–40% decline in the striatal TPH activity 3 h and 7 days after treatment. This finding is similar to the effects of several other amphetamine analogs and such long-term changes in TPH activity are often associated with destruction of 5-HT neurons (Kleven et al., 1989). It is noteworthy that, unlike the other analogs, the striatal levels of 5-HT did not decline with TPH activity following multiple 4-methylaminorex treatment (fig. 2). This observation suggests that the effects of 4-methylaminorex on 5-HT systems are somewhat unique from the other amphetamine-related compounds, although the significance of this difference is presently unclear.

It is interesting that following a single 4-methylaminorex administration, recovery of TPH activity occurred 18 h after treatment, but was significantly decreased again by 7 days. One possible explanation for this finding is that the 3-h and 7-day effects on TPH activity are due to distinct mechanisms and the 18-h time point represents recovery from the short-term effect, but is too early for the expression of the long-term effect. As mentioned above, the long-term decline in TPH activity may be associated with the loss of 5-HT neurons; however, the present findings are only suggestive that 4-methylaminorex can be neurotoxic and this hypothesis needs to be confirmed by additional histological analysis. The mechanism responsible for the acute decline of TPH activity (3 h after a single 4-methylaminorex dose) was investigated in the present study. As we previously reported for methamphetamine, MDMA and other amphetamine analogs (Stone et al., 1989), incubation in a reducing environment of cortical tissue from 4-methylaminorex-treated rats completely reversed the drug-induced reduction in TPH activity (fig. 4). This finding suggests that, like other analogs, a single 4-methylaminorex treatment initially alters TPH activity by oxidizing the enzyme; an effect which can be restored by exposing the tissues for 24 h to reducing factors.

It is of significance that no hint of long-term effects on striatal dopaminergic systems was observed after 4-methylaminorex administration. Although short-term

neurochemical changes previously reported (increased levels of DA metabolites 30 min after treatment; Bunker et al., 1990) suggest that 4-methylaminorex causes substantial DA release, no changes in DA parameters were observed 7 days after a single (fig. 2) or multiple (fig. 5) administrations of this drug. Due to the very potent epileptogenic effect of this drug at doses of 15 mg/kg or greater, we were unable to evaluate the dopaminergic toxicity of this compound at higher doses. Nevertheless, using the 10 mg/kg dose for comparison, it appears that effects of 4-methylaminorex on DA pathways are more like those of the ring-substituted amphetamines (such as MDMA) than like methamphetamine (Stone et al., 1986).

Despite the apparent absence of long-term effects on dopaminergic pathways, several observations in the present study demonstrate that 4-methylaminorex causes increased activity of these systems. Firstly, 3 h after a single dose of 4-methylaminorex, striatal tyrosine hydroxylase activity temporarily declined (fig. 3). This enzyme change was not due to a direct effect of 4-methylaminorex because addition of this drug directly to striatal tissue samples being assayed did not alter the tyrosine hydroxylase activity. However, the short-term decline in tyrosine hydroxylase activity might represent a feedback response to increased DA release induced by 4-methylaminorex. Secondly, 3 h following multiple 4-methylaminorex doses, there was still an increase in DOPAC levels suggesting an increase in DA turnover (fig. 6). It should be mentioned that a significant concurrent rise in striatal DA levels was also observed; the significance of this change is not presently clear. Thirdly, and perhaps the most convincing evidence from the present study, was the dramatic response of nigral neuropeptide systems to multiple administrations of 4-methylaminorex. A similar dosing protocol with MDMA or methamphetamine also substantially increases the nigral levels of neurotensin, dynorphin and substance P 18 h after treatment; comparable changes in all three peptides were observed 18 h after 4-methylaminorex treatment (fig. 6). Of significance is the observation that the degree of increase in neurotensin, dynorphin and substance P is like that which occurs after similar doses of the other amphetamine analogs (Ritter et al., 1984; Letter et al., 1987a; Hanson et al., 1988; Hanson et al., 1989). Because these changes in peptide content are dose-dependent for other amphetamine-like drugs, and have been proven to reflect the DA-releasing property of these stimulants and not other monoamine effects (Letter et al., 1987a; Hanson et al., 1988), the present findings suggest that 4-methylaminorex releases DA in a comparable manner. The 4-methylaminorex-induced changes in nigral peptide content were only temporary (fig. 7) and likely not due to neurotoxicity, but probably caused by the reversible pharmacological actions of this drug. Because of this finding, it is not surprising that 4-methylaminorex causes amphetamine-like increased locomotor activity and stereotypic behavior and occasionally is substituted for amphetamine derivatives in the street (Drug Control Section, 1988).

In summary, 4-methylaminorex affected both 5-HT and DA systems. The present findings and those of Bunker et al. (1990) suggest that 4-methylaminorex can cause long-term changes in serotonergic systems which may be due to neurotoxicity. As with some of the other amphetamine analogs, 4-methylaminorex appears to cause oxidative stress resulting in a quick but reversible decline in TPH activity. Although apparently not toxic to DA systems, 4-methylaminorex does cause profound increases in dopaminergic activity resulting in rapid and short-term changes in DA metabolites (Bunker et al., 1990; fig. 6). Further evidence of the 4-methylaminorex-induced increase in dopaminergic activity is the dramatic rise in striatal and nigral neuropeptide levels which occurs after acute (Bunker et al., 1990) and multiple (fig. 7) administrations. Because of these neurochemical findings, it is not surprising that 4-methylaminorex causes amphetamine- and cocaine-like effects in behavior models (Drug Control Section, 1988). Although not directly addressed in the present study, 4-methylaminorex is a very potent convulsant agent; after doses of 15 mg/kg approximately 50% of the treated animals experienced seizure activity. It is not clear from the present study if any of the neurochemical responses observed contribute to the epileptogenic properties of this drug of abuse.

Acknowledgement

This work was supported by U.S. Public Health Service Grants, DA 00869 and DA 04222.

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