Neurochemical effects of an acute treatment with 4-methylaminorex: a new stimulant of abuse

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4-Methylaminorex (4-MAX) is an amphetamine analog which has recently gained attention due to its potential as a stimulant of abuse. The present study characterized the acute neurochemical changes elicited after a single dose of 4-MAX. Thus, dose-response and time-response studies were conducted in order to assess the effects of this drug on monoaminergic and neuropeptide systems in extrapyramidal and limbic structures. The most dramatic responses in the dose-effect experiments (animals killed 3 h after treatment) were a 2-fold increase in neostriatal homovanillic acid levels and a decrease in neostriatal tryptophan hydroxylase activity to 33% of control in the 20 mg/kg group. Because all animals in the 20 mg/kg group experienced convulsions, 10 mg/kg was used for the time-response studies. The most striking effects in these studies included a reduction in dopamine concentrations to 71% of control, and an increase to 270% of control in the concentrations of dihydroxyphenylacetic acid 30 min after 4-MAX administration. In addition, neostriatal neurotensin and dynorphin A levels increased to approximately 200 and 400% of control, respectively, 18 h after a 10 mg/kg dose. These data suggest that 4-MAX is a potent dopamine releaser, which decreases tryptophan hydroxylase activity in a manner similar to other amphetamine-related drugs. However, in contrast to other amphetamine analogs, 4-MAX has potent convulsant actions.

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

1. Introduction

4-Methylaminorex (2-amino-4-methyl-5-phenyloxazoline; 4-MAX) was described in 1963 as an indirect-acting sympathomimetic drug with anorectic properties (Poos et al., 1963; Roszkowski and Kelly, 1963; Yelnosky and Katz, 1963). The cis-(+)isomer has been confiscated from illicit clandestine laboratories; it is easily synthesized in a one-step reaction from the condensation of phenylpropanolamine with cyanogen bromide. If norpseudoephedrine is substituted for phenylpropanolamine, the trans isomer is formed (Poos et al., 1963). Both the cis and trans isomers of 4-MAX are purported to have similar stimulant and anorectic properties which are comparable to those of amphetamine (Roszkowski and Kelly, 1963; Yelnosky and Katz, 1963).

4-MAX is similar in chemical structure to pemoline, which is a Schedule IV CNS stimulant, and aminorex. Aminorex was marketed as an anorectic in Europe in November, 1965, but was withdrawn in October, 1968 due to associated severe primary pulmonary hypertension, (Gurtner, 1985). The suggested mechanism of action of this potentially fatal side effect was chronic pulmonary vascular obstruction due to arteriopathy. The mean time from initial symptoms (dyspnea, exercise in-

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tolerance, etc.) to hospitalization was 10 months. An idiosyncratic pharmacokinetic explanation was proposed, as hypertensive pulmonary vascular disease was not demonstrated in a study on rats and dogs (Kay et al., 1971). Consequently, because of the chemical similarity to aminorex, 4-MAX might also cause pulmonary complications, although no studies have been reported which demonstrate such an association.

Recently, 4-MAX has gained attention as a drug of abuse. Users refer to it by various names, including U4EA, EU4EA or U4Euh, and on occasion it has been masqueraded as methamphetamine (METH), 'speed' or cocaine (Drug control section, 1988). In a preliminary study with monkeys trained to lever press for cocaine, 4-MAX was self-administered over saline by 3/3 rhesus monkeys (Drug control section, 1988). Additionally, 4-MAX was self-administered in a manner similar to that of cocaine. Users have described the effects of 4-MAX to be like those of amphetamine and cocaine.

Under emergency status, the cis isomer of 4-MAX was temporarily assigned to the Schedule I drug category of the Controlled Substances Act on October 15, 1987. Due to the high potential for abuse of this substance, a final decision was made in April, 1989 to retain the Schedule I classification for 4-MAX. Illegally manufactured 4-MAX has been confiscated by authorities in Florida, California, Pennsylvania, and one death attributed to 4-MAX has been documented in Florida (Drug control section, 1988; Davis and Brewster, 1987). The autopsy report from Florida described death due to respiratory paralysis, visceral congestion, and cerebral and pulmonary edema. Ubsubstantiated reports of convulsive seizures have also been noted following the use of this amphetamine-like stimulant.

Although 4-MAX appears to cause stimulant-like behavior, nothing is known about its pharmacological or toxicological actions on the central nervous system. In spite of the paucity of information concerning the CNS effects of 4-MAX, authorities fear that the accessibility of precursors, and the ease of synthesis of this compound will lead to more widespread abuse of 4-MAX. Consequently, it is important that the pharmacology and toxicology of 4-MAX be elucidated. To assess the neurochemical responses of 4-MAX, and to compare its effects with those of other stimulant drugs of abuse (e.g. METH and 3,4-methylenedioxymethamphetamine (MDMA)), we administered a single dose of 4-MAX s.c. and evaluated monoaminergic parameters as well as changes in the neuropeptides, dynorphin A and neurotensin. These parameters were selected for evaluation because they are known to be altered by administration of other amphetamine analogs.

2. Materials and methods

Male Sprague-Dawley rats (150-220 g) were housed three to four per cage 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-MAX (supplied by the National Institute on Drug Abuse) was dissolved in 0.9% saline and administered s.c. in single dose of either 5, 10 or 20 mg/kg (expressed as the free base). The control animals were injected s.c. with an equivalent volume of the vehicle alone. Rats were killed within a 4-h period at mid-day by decapitation, 30 min-18 h after injection of the drug; groups for each time-period and dose included both 4-MAX-treated and saline-treated (control) rats. Immediately after decapitation the brain was removed and placed on ice, and the neostriatum, hippocampus and frontal cortex regions were dissected bilaterally and stored at −80°C until assayed.

2.2. Enzyme assays

One of the paired tissues from each region 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 (Ichiyama et al., 1970; Sitaram and Lees, 1978) as described by Hotchkiss et al. (1979). In some cases, identical 10-μl aliquots (neostriatal tissue only) were diluted to 50 μl with glass-distilled water and analyzed for activity of tyrosine hydroxylase (TH), according to the method of Nagatsu et al. (1964) by measuring the formation of $[^3H]H_2O$. [^{3}H]Tyrosine and $[^3H]H_2O$ were separated according to the method of Reinhard et al. (1986). The incubation medium in each tube (100 μl total volume) contained 200 000 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.

2.3. Determination of concentrations of monoamines and metabolites of monoamines

Neostriatal concentrations of 5-hydroxytryptamine (5-HT) and its primary metabolite, 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA) and its major metabolites dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA), 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 × *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 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.

Norepinephrine (NE) concentrations were estimated according to a modification of the method described by Mefford (1981). The hippocampus was weighed and homogenized in 800 μl of 0.2 N perchloric acid containing 75 nm 3,4-dihydroxybenzylamine using a Potter-Elvejhem homogenizer. A 400-μl aliquot was transferred into a 1.5-ml microcentrifuge tube containing 10-14 mg of alumina (prepared according to Anton and Sayre, 1962) and 1.1 ml of 0.5 M Tris[hydroxymethyl]aminomethane buffer (pH 8.6). The supernatant was discarded after mixing 15 min by inversion, and 1.5 ml of 0.1 mM sodium acetate was used to wash the alumina. After discarding the supernatant, 120 μl of 0.2 N perchloric acid containing 0.1 mM EDTA was added to the alumina, mixed, and centrifuged for 30 min at 13 000 × *g*. The supernatant was collected, stored at −80 °C, and assayed within 3 days. Using a Varian liquid chromatograph (model 5000) equipped with a Bioanalytical System amperometric detector set at a potential of +0.9 V (versus Ag/AgCl reference electrode), a 50-μl aliquot was injected onto a 12.5-cm Whatman PartiSphere C18 reversed phase column connected to another PartiSphere column. The mobile phase, pumped at a flow rate of 1.1 ml/min consisted of 0.1 M monobasic sodium phosphate, 0.1 mM EDTA, 0.2 mM octanesulfonic acid (pH 3.0) and 4% methanol.

2.4. Neuropeptide assays

Neostriatal tissues were homogenized in 0.75 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 × *g*, and the resulting supernatant was removed for lyophilization. Samples were reconstituted in 0.75 ml phosphate-buffered saline with 0.1% gelatin (0.1 M monobasic sodium phosphate, 0.9% sodium chloride, and 0.1% sodium azide; pH 7.4). Neurotensin (NT) and dynorphin A-(1-17) (Dyn) concentrations were determined by

radioimmunoassay as previously reported (Letter et al., 1987; Hanson et al., 1988). The concentrations were measured as picograms of NT or Dyn-like immunoreactivity per milligram protein.

2.5. Statistics

Data presented are the means ± S.E.M. and expressed as a percentage of corresponding saline-injected controls. An ANOVA followed by multiple comparisons analysis with the Scheffe F-test were used to evaluate the data in figs. 1 and 4, while the data in figs. 2, 3 and 5 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. Dose-response of monoamine systems

Three hours after administration of 4-MAX, neostriatal HVA concentrations were significantly elevated to 200% of control values in animals treated with 20 mg/kg of the drug (fig. 1A). A small but significant elevation in neostriatal DA concentrations was detected with the 5 mg/kg dose. No alterations in (TH) activity or the concentration of DOPAC were detected with any of the treatments.

Tryptophan hydroxylase activity declined significantly after 4-MAX in a dose-dependent manner (74% of control with 5 mg/kg to 37% of control with 20 mg/kg) (fig. 1B), while a reduction of 5-HT content was observed (63% of control) with the 20-mg/kg dose. Norepinephrine levels in the hippocampus of animals treated with 4-MAX were not significantly lowered compared to control values, but levels of this monoamine did differ significantly between the 5 and 20 mg/kg-treated groups (fig. 1C). The hippocampus was used to assess the response of the noradrenergic system to 4-MAX since neostriatal norepinephrine levels are much lower and difficult to detect with precision.

Behaviorally, animals which received low doses (5 mg/kg) of 4-MAX displayed increased locomo-

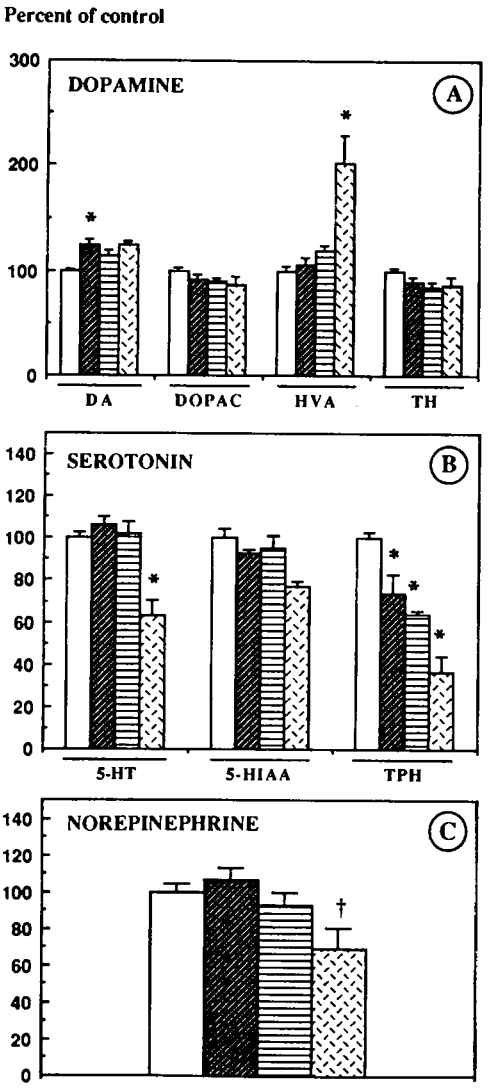

Fig. 1. Response of monoamine systems to a single injection of 5, 10 or 20 mg/kg of 4-MAX. Dopaminergic (DA) (A) and serotonergic (B) parameters were measured in the neostriatum, while norepinephrine (NE) concentrations (C) were measured in the hippocampus. In animals killed 3 h after treatment, the mean control concentrations of DA, NE, DOPAC, HVA, 5-HT and 5-HIAA were 10.7, 1.16, 0.70, 0.62, 0.63 and 0.48 μg/g tissue, respectively. The mean control values for TH and TPH activity were 1486 nmol of hydroxylated tyrosine and 15.43 nmol of hydroxylated tryptophan/h per g tissue, respectively. N = 4-12 for all groups except the 20 mg/kg group where n = 3-4 due to mortality. * $P < 0.05$ compared to corresponding controls. † $P < 0.05$ compared to the 5 mg/kg group. □ Control, ▨ 5 mg/kg, ▤ 10 mg/kg and ▩ 20 mg/kg 4-MAX.

tor activity and rearing compared to control animals. The animals which received 10 mg/kg initially experienced increased locomotion and rearing, and within 10-15 min they expressed amphetamine-like stereotypic behaviors for the duration of the study. All animals which received 20 mg/kg of 4-MAX experienced clonic seizures within the first hour after treatment. No clonic seizures were seen in rats given 5 or 10 mg/kg of 4-MAX.

Interestingly, mortality was observed in the majority of animals which developed 4-MAX-induced seizures: death occurred 3-18 h following drug administration. In contrast, all animals which did not develop seizures survived. In order to avoid inducing convulsions, and because the 10 mg/kg dose appeared to be a sufficient dose to evoke significant monoaminergic and related enzymatic changes, this dose of 4-MAX was used for the remainder of this study.

3.2. Recovery of monoamine systems

As shown in fig. 2, 30 min after a s.c. injection of 10 mg/kg of 4-MAX, DA levels were significantly reduced to 71% of control values, while DOPAC and HVA concentrations were markedly elevated to 269 and 144% of control levels, respectively. In contrast, 3 h after 4-MAX administration DA concentrations were significantly elevated, while DOPAC levels were lowered. HVA concentrations remained elevated at this 3-h timepoint. However, 8 h after drug administration no differences from control values were seen in DA, DOPAC or HVA levels.

Only 30 min after 4-MAX administration were 5-HT concentrations significantly altered (77% of control values) while 5-HIAA levels were not significantly different from control values at any time examined after drug administration (fig. 3). The drug-induced changes in TPH activity were similar to those seen in the previous study (fig. 1) indicating a significant depression in activity (approximately 63% of control in both experiments) 3 h after drug administration. No change in TPH activity was observed 30 min after injection; by 8 h the activity of this enzyme appeared to be recovering.

3.3. Cortical and hippocampal response

In order to assess the effects of 4-MAX on other brain structures, TPH activity was studied in the hippocampus and frontal cortex. The data presented in fig. 4 demonstrate that TPH activity declined in a dose-dependent pattern in both

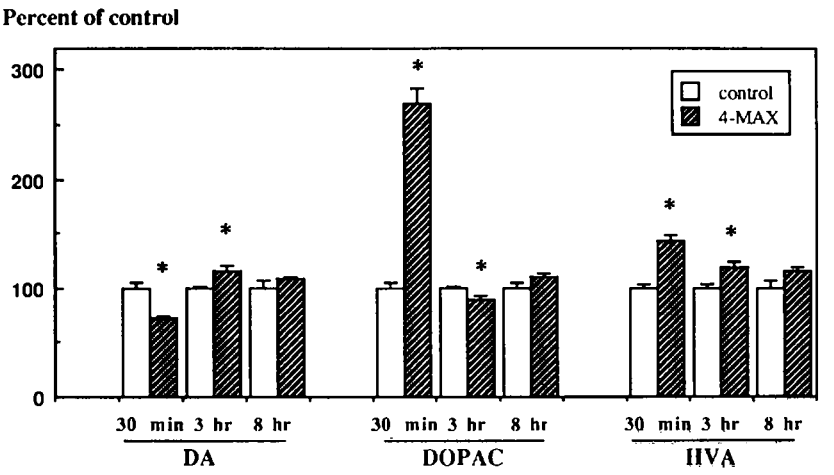

Fig. 2. Recovery of the neostriatal dopaminergic system 30 min, 3 h and 8 h following a single injection of 4-MAX (10 mg/kg). The concentrations of DA in the saline-controls at 30 min, 3 h and 8 h, were: 10.96, 10.70 and 7.30 μg/g tissue, respectively. The concentrations of DOPAC in saline-treated controls at the above time points were: 0.498, 0.702 and 1.162 μg/g tissue, respectively. HVA concentrations in saline controls were: 0.477, 0.621 and 0.59 μg/g tissue, respectively (n = 6-12). * $P < 0.05$ compared to corresponding controls.

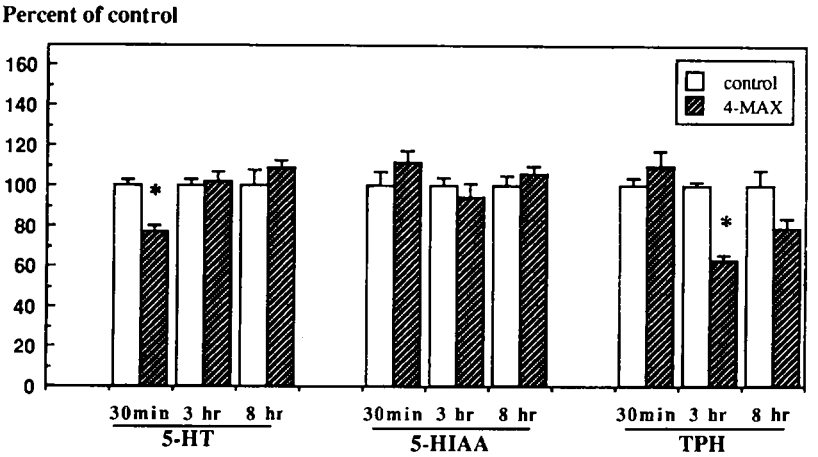

Fig. 3. Recovery of the neostriatal serotonergic system 30 min, 3 h and 8 h following a single injection of 4-MAX (10 mg/kg). Concentrations of 5-HT in saline-treated controls at 30 min, 3 h and 8 h were: 0.523, 0.627 and 0.38 μg/g tissue, respectively. 5-HIAA concentrations in controls were: 0.43, 0.482 and 0.442 μg/g tissue, respectively. TPH activity of these same controls were: 20.43, 16.63 and 26.15 nmol hydroxylated tryptophan/h per g of tissue, respectively (n = 6-12). * $P < 0.05$ compared to corresponding controls.

structures in a similar manner to that observed in the neostriatum. The decline in cortical and hippocampal TPH activities following 20 mg/kg of 4-MAX was 34 and 45% of control, respectively.

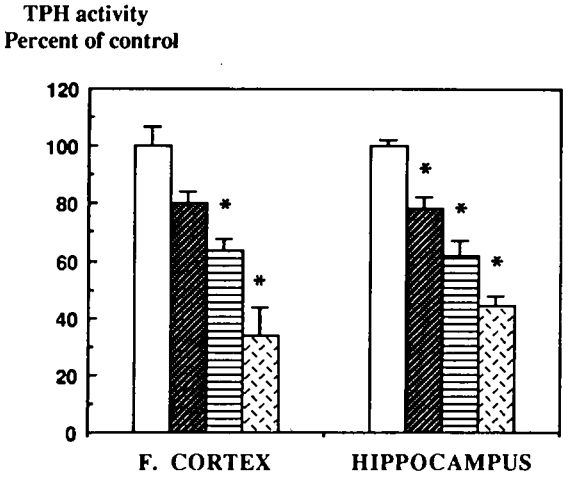

Fig. 4. Effects of a single dose of 5, 10 or 20 mg/kg of 4-MAX on TPH activity in the frontal cortex and hippocampus. Animals were killed 3 h after treatment. The cortical and hippocampal TPH activiy of the saline-controls were 59.3 and 52.2 nmol of hydroxylated tryptophan/h per g of tissue, respectively (n = 6-12). * $P < 0.05$ compared to corresponding controls. ☐ Control, ▨ 5 mg/kg, ▤ 10 mg/kg and ▩ 20 mg/kg 4-MAX.

3.4. Neostriatal neuropeptide response

Our observations suggested that administration of 4-MAX significantly enhanced neostriatal dopaminergic activity. This possibility was further evaluated by measuring the response of neostriatal neuropeptide systems which are regulated by dopaminergic activity (Hanson et al., 1988; Letter

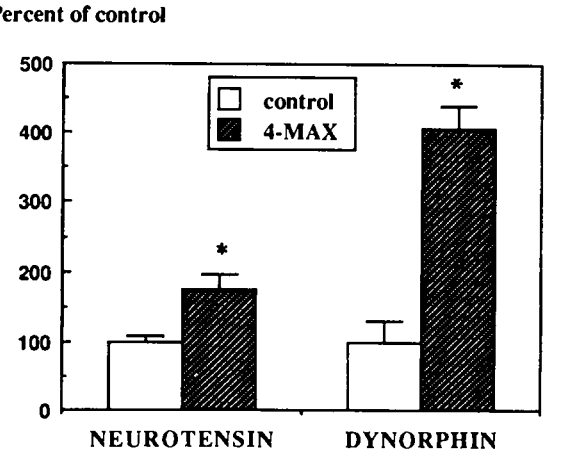

Fig. 5. Effect of a single dose of 4-MAX (10 mg/kg) on neostriatal neurotension and dynorphin A levels 18 h after injection. The concentrations of neurotensin and dynorphin A of the saline controls were 67 and 170 pg/mg protein, respectively (n = 6). * $P < 0.05$ vs. corresponding controls.

et al., 1987; Merchant et al., 1987). Eighteen hours after a single dose of 4-MAX (10 mg/kg), neostriatal levels of neurotensin and Dyn were markedly elevated (173 and 406% of control, respectively) (fig. 5). Such dramatic and rapid increases in the concentrations of these peptides are consistent with a potent drug-induced rise in dopaminergic activity.

4. Discussion

The results of this study indicate that 4-MAX has profound effects on monoaminergic and neuropeptide systems in the rat brain. Thirty minutes after administration, 4-MAX elicits a profound increase in neostriatal concentrations of the DA metabolites, DOPAC and HVA (fig. 2). Such a response suggests that this drug initially causes a dramatic release of DA from presynaptic neurons. Since an increase in DA release elevates neostriatal neuropeptide concentrations (Hanson et al., 1988; Letter et al., 1987; Merchant et al., 1987), the DA-releasing property of 4-MAX was further substantiated by the observation that 200 and 400% increases in the neostriatal levels of dynorphin and neurotensin occurred following treatment with this drug (fig. 5). The acute effect of 4-MAX on dopaminergic parameters is notably distinct from that of other amphetamine analogs. For example, a single comparable dose of amphetamine or MDMA produces initial elevations in neostriatal DA and HVA, while DOPAC concentrations are reduced in the first hour after administration (Stone et al., 1987; Kuczenski, 1980). The dopaminergic response of most amphetamine-like drugs is thought to be influenced by the inhibition of the enzyme, monoamine oxidase, thereby preventing the metabolism of DA to DOPAC (Miller et al., 1979). Because of the dramatic increase in DOPAC levels following 4-MAX administration, it is likely that this drug has little effect on the activity of this enzyme.

The most dramatic effect of 4-MAX on the serotonergic system was the substantial reduction of neostriatal TPH activity to approximately 40% of control 3 h after the highest dose (20 mg/kg) (fig. 1). THP activity in other brain regions, namely hippocampus and frontal cortex, was also dramatically decreased at this time-point, suggesting all CNS serotonergic systems were affected by 4-MAX in a similar manner (fig. 4). Following a dose of 10 mg/kg, the decline in neostriatal TPH activity appeared to be recovering by 8 h (fig. 2). Serotonin levels were significantly reduced 30 min after a 10 mg/kg treatment but returned to control levels within 3 h. In comparison, equivalent doses of METH and MDMA elicit similar declines in TPH activity by 3 h after drug treatment, nevertheless, a single dose of METH or MDMA results in a more prolonged TPH depression than that observed following 4-MAX treatment. The mechanism(s) of acute TPH inactivation by 4-MAX are likely similar to that of METH and MDMA, which has been postulated to involve a DA-mediated state of oxidative stress induced by these drugs (Stone et al., 1989). However, the relatively rapid recovery of TPH activity following 4-MAX administration (back to 80% of control by 8 h) (fig. 3) suggests this agent is significantly less neurotoxic than METH (Hotchkiss et al., 1979) or MDMA (Stone et al., 1987). Additional studies must be conducted in order to assess fully the neurotoxic potential of 4-MAX.

Like METH, 4-MAX elicited a decline in neostriatal 5-HT levels initially; recovery occurred within the first 24 h after treatment (Peat et al., 1985). Comparable doses of MDMA, however, cause a permanent decline in 5-HT concentrations which may reflect greater serotonergic toxicity resulting from the administration of this drug (Stone et al., 1987). The decline in 5-HT levels 30 min after 4-MAX administration is likely due to release of this monoamine and its subsequent metabolism, while the decrease of 5-HT and 5-HIAA tissue content with 20 mg/kg of 4-MAX (fig. 1), occurred 3 h after treatment and possibly reflects a decline in synthesis due to drug-induced TPH inhibition. Additional experiments are necessary to elucidate these mechanism(s) further.

Norepinephrine levels in the hippocampus were significantly lowered 3 h after treatment with 4-MAX following the highest dose (20 mg/kg) when compared to the 5 mg/kg group (fig. 1). Even though the difference in NE levels between the 20 mg/kg group and control did not reach signifi-

cance with the Scheffe test, it is likely that treatment with 4-MAX does cause a reduction in NE concentration. This observation is consistent with reports that a single (15 mg/kg) dose of METH lowers NE levels (Michel Johnson, personal communication), and demonstrates that all monoaminergic systems are altered by 4-MAX administration.

In conclusion, these findings demonstrate that while 4-MAX has neurochemical effects on monoaminergic systems similar to that of several other amphetamine-like drugs of abuse, there are important differences. For example, the response of DA systems to 4-MAX is somewhat unique in that this drug appears not to inhibit monoamine oxidase. Behaviorally, we observed that 4-MAX has stimulant properties which produce increased locomotor and stereotypic behavior similar to that caused by amphetamine and its analogs. However, an important distinction is the propensity of 4-MAX to evoke seizure activity at relatively low doses which do not promote seizures by other amphetamine derivatives. This potent convulsant property of 4-MAX has important implications for the drug-abusing population and is currently being characterized in our laboratory. These differences likely have important clinical implications in understanding and treating individuals who abuse this compound, and suggest that additional study of this drug is warranted.

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