Effects of chronic treatment of rats with "designer" amphetamines on brain regional monoamines

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(+)-Amphetamine and two structurally related analogues, 4-methoxyamphetamine and a recent "designer drug," 4-ethoxyamphetamine, were given to rats via subcutaneous osmotic minipumps for 1–14 days. Regional brain levels of the drugs as well as monoamine neurotransmitters and some of their major acidic metabolites were determined. Amphetamine produced depletions of dopamine in the striatum after at least 3 days of treatment but not in the nucleus accumbens or olfactory tubercle, even after 14 days of treatment. In contrast, the two ring-substituted amphetamine analogues increased levels of the monoamines and decreased levels of their acid metabolites. These data indicate that the two ring-substituted amphetamine analogues, at least one of which is a potent hallucinogen, have potent monoamine oxidase inhibition properties that are sustained during chronic treatment. Furthermore, these two compounds do not share amphetamine's regionally selective neurotoxic effects on dopamine-releasing terminals, even though brain and striatal drug levels are the same or higher than those of amphetamine.

Key words: (+)-amphetamine, 4-methoxyamphetamine, 4-ethoxyamphetamine, designer amphetamines, monoamines, rats, chronic treatment.

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L'(+)-amphétamine et deux analogues structuraux, la 4-méthoxyamphétamine et une nouvelle «drogue de confection», la 4-éthoxyamphétamine, ont été administrées à des rats par des minipompes osmotiques sous-cutanées pendant 1–14 jours. Les taux régionaux des drogues ainsi que des neurotransmetteurs de monoamine et de certains de leurs principaux métabolites acides ont été déterminés dans le cerveau. L'amphétamine a provoqué des déplétions de dopamine dans le striatum après au moins 3 jours de traitement, mais ces déplétions n'ont pas été observées dans le noyau accumbens ni dans le bulbe olfactif, même après 14 jours de traitement. A l'opposé, les analogues de l'amphétamine à deux anneaux substitués ont augmenté les taux des monoamines et diminué ceux de leurs métabolites acides. Ces données indiquent que les analogues à deux anneaux substitués de l'amphétamine, dont au moins un est un puissant hallucinogène, ont vis-à-vis des monoamines oxydases de très fortes propriétés d'inhibition qui sont maintenues lors d'un traitement chronique. De plus, ce deux composés ne partagent pas les effets neurotoxiques régionalement sélectifs de l'amphétamine sur les terminaisons libérant la dopamine, même si les taux des drogues dans le striatum et le cerveau sont identiques à ceux de l'amphétamine ou plus élevés que ceux-ci.

Mots clés : (+)-amphétamine, 4-méthoxyamphétamine, 4-éthoxyamphétamine, amphétamines de confection, monoamines, rats, traitement chronique.

[Traduit par la rédaction]

Introduction

4-Ethoxyamphetamine (EA) is a compound with potential as a drug of abuse. Quantities of this compound were seized by the Canadian police in 1987 from an illicit laboratory that was found to be synthesizing "designer" amphetamine (AM) compounds, and subsequently identified by the Drug Identification Division of Health and Welfare Canada. As a result there is an interest in determining the neurochemical profile of this drug, including its potential as a central monoamine neurotoxin. It has structural similarity to AM, a potent psychomotor stimulant without direct hallucinogenic effects on acute administration, and 4-methoxyamphetamine (MA), an AM analogue with minor stimulant but major hallucinogenic properties (Shulgin 1978), but little is currently known concerning the properties of EA.

A primary purpose of this study was to determine whether or not EA would produce regionally specific depletions of dopamine (DA) or serotonin (5-hydroxytryptamine, 5-HT), as has been found for DA following chronic continuous treatment regimens with AM (Eison et al. 1983; Ellison et al. 1978; Nwanze and Jonsson 1981), for 5-HT with 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy," Commins et al. 1987; Ricaurte et al. 1988*a*, 1988*b*), or for both DA and 5-HT with methamphetamine (Ricaurte et al. 1980, 1984). Such depletions produced by EA would provide evidence for a neurotoxicity potential of this compound, as long-term depletions of the monoamines produced by AM, methamphetamine, and MDMA have been associated with degeneration of DA- and (or) 5-HT-releasing terminals. While depletions of these

ABBREVIATIONS: AM, amphetamine; EA, 4-ethoxyamphetamine; MA, 4-methoxyamphetamine; DA, dopamine; NA, noradrenaline; 5-HT, 5-hydroxytryptamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; MDMA, 3,4-methylenedioxymethamphetamine; HPLC-EC, high-pressure liquid chromatography with electrochemical detection; GC-ECD, gas chromatography with electron capture detection.

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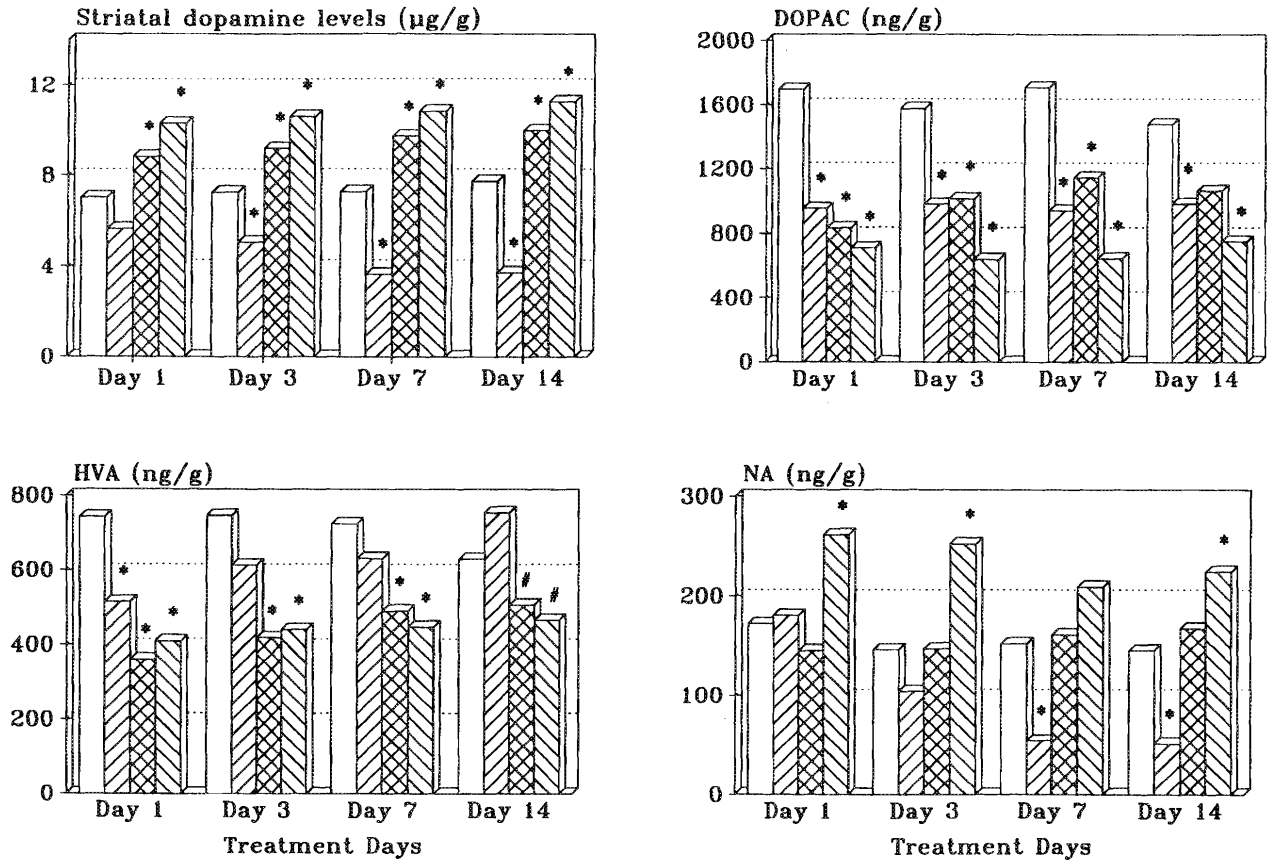

FIG. 1. Levels of dopamine, DOPAC, HVA, and NA in the striatum, expressed as a proportion of tissue weight, after different durations of subcutaneous infusions of vehicle (□), AM (▨), MA (▩), or EA (▧) at the dose of 40 µmol/day for each drug. *, significantly different from vehicle, HSD post-hoc test, $p < 0.05$; #, significantly different from AM, HSD post-hoc test, $p < 0.05$.

neurotransmitters is not sufficient evidence to enable unequivocal conclusions to be drawn concerning neurotoxic effects of the drugs on these monoaminergic systems, it has been clearly established that such depletions accompany neurotoxicity of a variety of AM analogues. Therefore, the absence of such depletions would indicate a lack of neurotoxic effects on these monoamine-containing neurons, while the presence of such depletions would be evidence for neurotoxic effects, to be verified by future histochemical work.

The present experiments assessed the effects of chronic administration of EA, in comparison with AM and MA, on brain regional concentrations of putative neurotransmitter monoamines and their major acidic metabolites, using high-pressure liquid chromatography with electrochemical detection (HPLC-EC). A dose of the AM analogues equimolar to doses of AM that have previously been found in this laboratory to produce dopamine depletions in the striatum using an identical treatment regimen was chosen. This dose (about 22 $mg \cdot kg^{-1} \cdot day^{-1}$) is slightly higher than the dose of AM required to produce extensive axonal degeneration in the striatum (Ryan et al. 1988). The specific treatment regimen (continuous subcutaneous infusions) has been previously shown to induce neurotoxic effects more readily than intermittent injection regimens, with depletions occurring within 3 days of initiation of treatment (Ellison et al. 1978; Gately et al. 1987; Ryan et al. 1988). The continuous infusion regimen was chosen to increase the possibility of observing neurotoxic effects of the novel AM analogue EA. In addition, striatal and brain levels of the drugs were determined with a gas chromatography procedure using electron capture detection (GC-ECD) to draw conclusions regarding relations of central tissue concentration to drug responses. AM was chosen as one comparison compound because of its structural relationship to EA and its psychomotor stimulant effects, while MA is devoid of psychomotor stimulant effects but is a potent hallucinogen (five times more potent than mescaline; Biel and Bopp 1978) with structural similarity to the ethoxy analogue.

Methods

The experiments consisted of giving continuous infusions at constant rates (5 µL/h *in vitro* test) of one of the drugs ((+)-AM sulfate, MA HCl, or EA HCl) at a dose of 40 µmol/day for a maximum of 14 days to male Sprague–Dawley rats (250–350 g). Control animals were given continuous infusions of vehicle (propylene glycol, neat). This treatment regimen was accomplished with the use of ALZA Alzet® osmotic minipumps (model 2ML2). The pumps were implanted subcutaneously in the dorsal midscapular area while the animals were under ether anaesthesia. Animals were housed in groups of two in 20 (w) × 42 (l) × 20 (h) cm plastic rat cages with heat-treated Aspen wood chips, with *ad libitum* access to food (Wayne® Rodent BLOX®) and water, under a 12-h light – 12-h dark cycle (lights on 07:00–19:00). Rats were adapted to the housing condition for at least 1 week before the beginning of drug treatments. Animals were inspected daily to ensure their health. Different groups of rats ($n = 8$) were killed by guillotine decapitation after 1, 3, 7, or 14 days of treatment between 09:00 and 14:00 while still receiving the drug. Equal numbers of rats from each drug group were randomly assigned to be

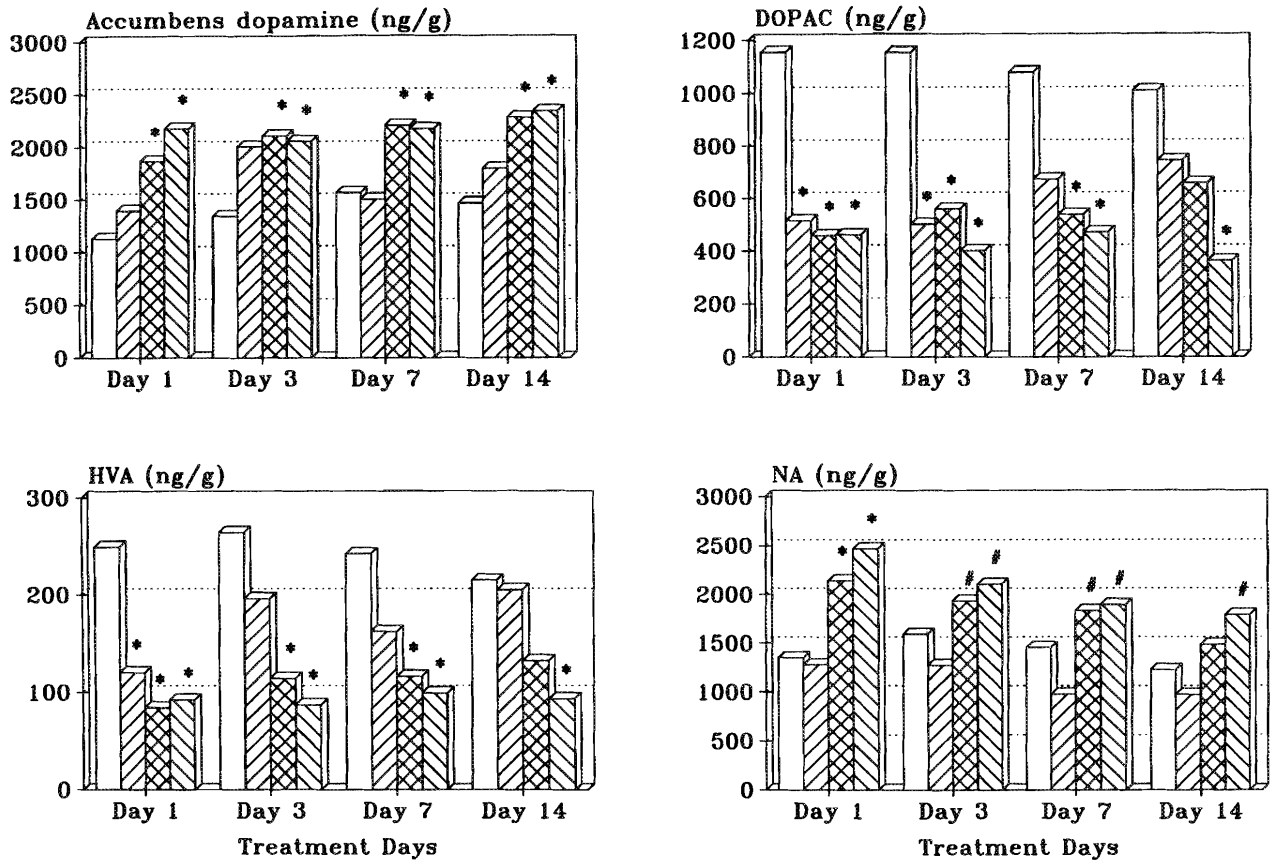

FIG. 2. Levels of dopamine, DOPAC, HVA, and NA in the nucleus accumbens septi, expressed as a proportion of tissue weight, after different durations of subcutaneous infusions of vehicle (□), AM (▨), MA (▩), or EA (▧) at the dose of 40 μmol/day for each drug. *, significantly different from vehicle, HSD post-hoc test, $p < 0.05$; #, significantly different from S, HSD post-hoc test, $p < 0.05$.

sacrificed on a specific day. Rats were killed by guillotine decapitation, and the brains were rapidly removed and placed on ice. A transverse cut was made between the mammillary bodies and the hypothalamus, with the caudal portion kept as part of the "residual" brain tissue. The corpus callosum was slit and a longitudinal cut was made to separate right from left brains. The olfactory tubercles were removed from the ventral surface. From the medial view, the area ventral to the striatum circumscribing the anterior commissure was removed as the nucleus accumbens. The striatum of each side was then gently scooped out. The rest of the brain tissue was included with the caudal portion initially removed as "residual" brain tissue. All tissue was frozen with solid carbon dioxide and kept at −80°C until the time of the assay. Each pair of bilateral regions was analyzed for content of monoamines and metabolites. Levels of DA and its acid metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), 5-HT and its major acidic metabolite 5-hydroxyindoleacetic acid (5-HIAA), and NA were assayed by HPLC-EC, following the procedure of Baker et al. (1987). The striatum and the residual brain tissue (all brain tissue other than the striatum, nucleus accumbens, and olfactory tubercle) were analyzed for levels of the AMs with a GC-ECD procedure (Baker et al. 1986), using 4-chloroamphetamine as a standard for AM and MA, and AM as the standard for EA. AM sulfate, MA HCl and EA HCl were supplied courtesy of Health and Welfare Canada, Drug Identification Division, Ottawa, and the compounds used as standards in the assays were purchased from Sigma Chemical Co., St. Louis, MO.

The data were analyzed by two-way analysis of variance, with the drug as one factor of four levels (vehicle, AM, MA, and EA) and time as the second factor with four levels. Individual comparisons were made using Tukey's honestly significant difference *t*-test (HSD), with the number of means compared obtained from a table for two-way ANOVA from Kiess (1989). The results of the individual comparisons are indicated in the figures. Pearson's correlations between body weights at the beginning of drug treatments and AM levels were calculated.

Results

Figures 1 through 5 depict the effects of the compounds on regional levels of monoamines and some of their acid metabolites. ANOVA revealed that there were significant drug−time interactions for many of the neurochemicals, but these were all restricted to the striatum: DA ($F_{9,112} = 3.57$, $p < 0.01$); HVA, ($F_{9,112} = 2.85$, $p < 0.01$); 5-HIAA ($F_{9,112} = 2.01$, $p < 0.05$); NA ($F_{9,110} = 3.04$, $p < 0.01$). Other striatal neurochemicals measured, as well as those from nonstriatal regions, exhibited significant drug effects, without time (duration of treatment) interactions or main effects of time. (*i*) Striatum: DOPAC ($F_{3,112} = 70.14$, $p < 0.001$); 5-HT ($F_{3,112} = 62.11$, $p < 0.001$); (*ii*) accumbens: DA ($F_{3,112} = 9.84$, $p < 0.001$); DOPAC ($F_{3,112} = 32.5$, $p < 0.001$); HVA ($F_{3,122} = 34.26$, $p < 0.001$); 5-HT ($F_{3,112} = 83.75$, $p < 0.001$); 5-HIAA ($F_{3,112} = 74.15$, $p < 0.001$); NA ($F_{3,112} = 55.18$, $p < 0.001$); (*iii*) olfactory tubercle: DA ($F_{3,112} = 16.56$, $p < 0.001$); DOPAC ($F_{3,112} = 76.76$, $p < 0.001$); HVA ($F_{3,112} = 34.26$, $p < 0.001$); 5-HT ($F_{3,112} = 69.89$, $p < 0.001$); 5-HIAA ($F_{3,112} = 134.2$, $p < 0.001$); NA ($F_{3,112} = 7.68$, $p < 0.001$).

AM significantly reduced DA levels in the striatum after 3−14 days of treatment (Fig. 1), but DA content in the

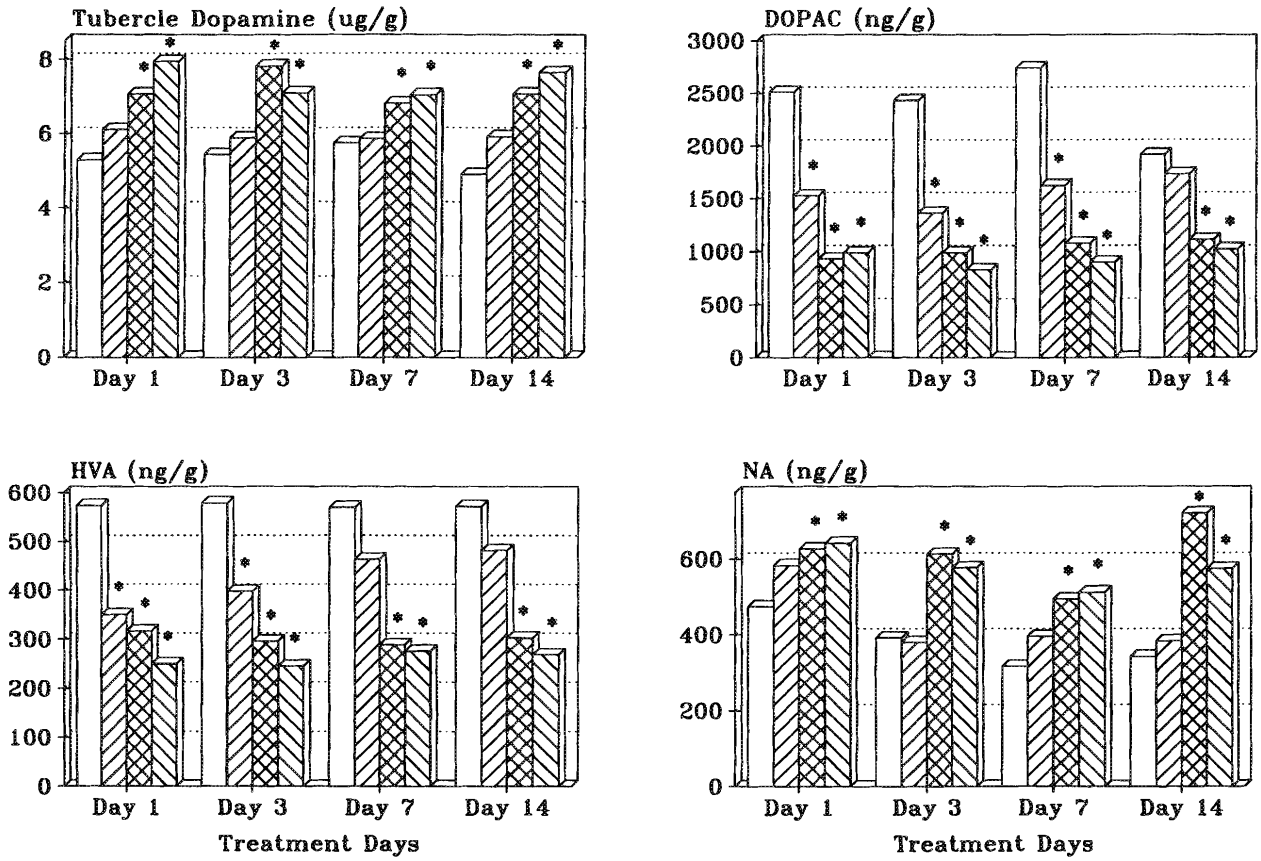

FIG. 3. Levels of dopamine, DOPAC, HVA, and NA in the olfactory tubercle, expressed as a proportion of tissue weight, after different durations of subcutaneous infusions of vehicle (□), AM (▨), MA (▩), or EA (▧) at the dose of 40 μmol/day for each drug. *, significantly different from vehicle, HSD post-hoc test, $p < 0.05$.

nucleus accumbens (Fig. 2) and olfactory tubercle (Fig. 3) were either not affected or slightly increased by AM. In contrast, both ring-substituted AM analogues consistently and significantly increased DA levels in all three brain regions and at all treatment durations. AM decreased DOPAC levels in all three regions (Figs. 1–3). Likewise, the substituted AMs decreased DOPAC levels in the three regions. Some apparent recovery of DOPAC levels was observed in the nucleus accumbens and olfactory tubercle, especially with AM, to a lesser extent with MA, and not at all with EA. However, it should be noted that no statistically significant effects of duration of treatment were observed in the ANOVA. HVA levels were decreased on the 1st day by AM in all three regions, but this effect of AM was absent by the 3rd (striatum, Fig. 1; accumbens, Fig. 2) or 7th day (olfactory tubercle, Fig. 3), again without a significant effect of treatment duration in the accumbens or tubercle. Both AM analogues decreased HVA in all three regions.

AM significantly reduced NA levels, but only in the striatum (Fig. 1), and only after 7 or 14 days of treatment. AM had no significant effects on NA in either the accumbens (Fig. 2) or olfactory tubercle (Fig. 3). In contrast, EA increased NA in all three brain regions, with the least pronounced effect in the accumbens, and MA increased NA in both accumbens and tubercle but not in the striatum. Accumbens NA was generally highest after 1 day of treatment with either ring-substituted AM analogue, with a progressive decrease reaching a nadir after 14 days ($F_{3,112} = 11.9$, $p < 0.001$).

5-HT was consistently elevated in all three brain regions across all treatment durations by EA (Figs. 4 and 5). MA increased 5-HT only in the accumbens. AM had no effect on 5-HT levels in any brain region at any treatment duration. The 5-HT metabolite 5-HIAA was significantly decreased in all brain regions (Figs. 4 and 5) and across all treatment durations by both methoxy- and ethoxy-substituted AMs, while AM produced only a slight (but consistent) decrease in 5-HIAA only in the olfactory tubercle.

Figure 6 displays the results of the drug determinations in striatal tissue, with the levels expressed as nanomoles of drug per gram of tissue. Because of a technical problem, some striatal tissue from AM-treated animals was lost, resulting in an n of 5 rather than 8. There was a significant main effect of drug ($F_{2,70} = 16.4$, $p < 0.001$) owing to a consistently higher level of EA than either MA or AM. There was no significant time (duration of treatment) effect ($F_{3,70} = 1.21$, $p > 0.1$) and the drug–time interaction was not significant ($F_{6,70} = 0.23$, $p > 0.1$). EA levels were consistently higher than those of both AM and MA over all durations of treatment, and the differences between AM and MA levels were not significant.

Figure 7 displays the results of the residual brain drug determinations, with the levels expressed as nanomoles of drug per gram of tissue. As with striatal drug levels, there was a significant main effect of drug ($F_{2,84} = 24.405$, $p < 0.001$) in residual brain tissue owing to a consistently higher level of EA than either MA or AM. There was no significant time (duration of treatment) effect ($F_{3,84} = 1.87$, $p > 0.1$) and the

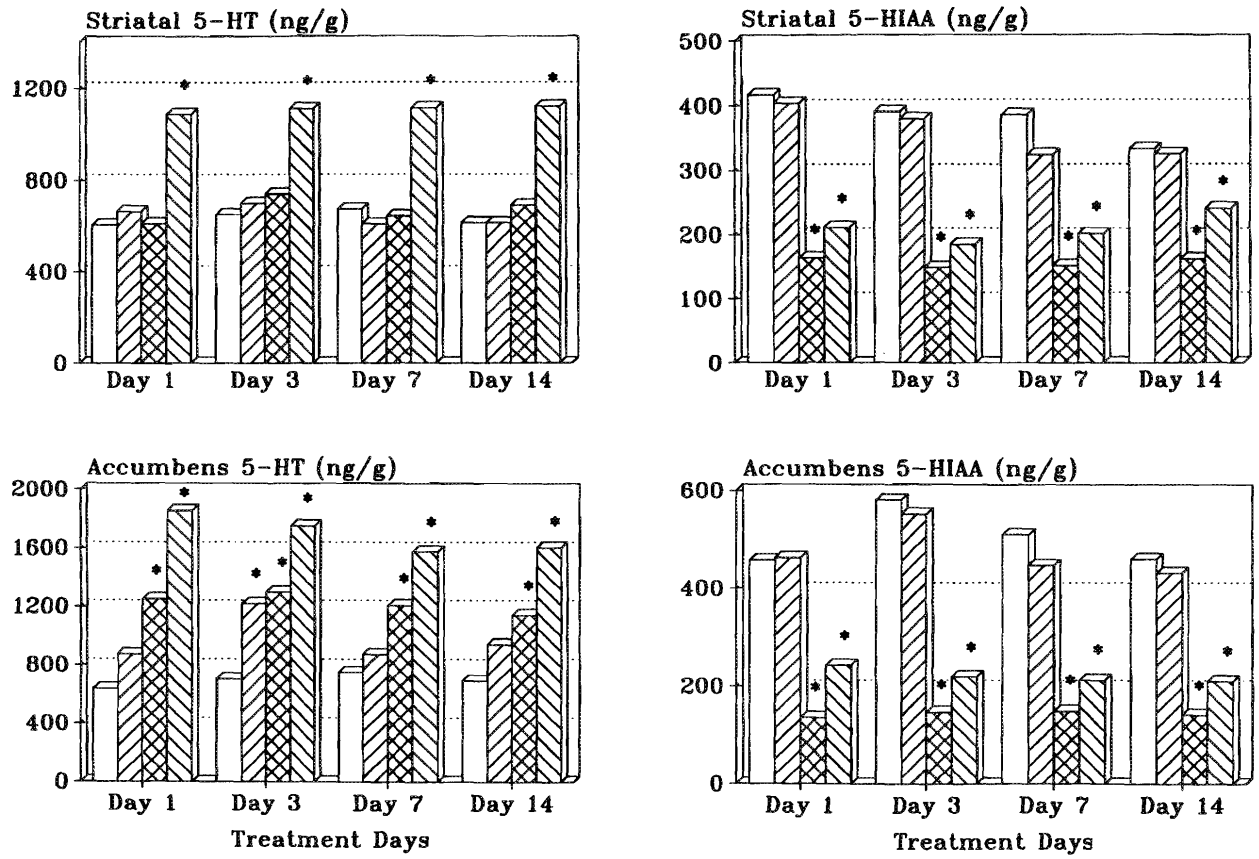

FIG. 4. Levels of serotonin (5-HT) and its metabolite (5-HIAA) in the striatum and nucleus accumbens septi, expressed as a porportion of tissue weight, after different durations of subcutaneous infusions of vehicle (□), AM (▨), MA (▩), or EA (▧) at the dose of 40 μmol/day for each drug. *, significantly different from vehicle, HSD post-hoc test, $p < 0.05$.

drug−time interaction was not significant ($F_{6,84} = 2.00$, $p = 0.075$) at $\alpha = 0.05$. EA levels were consistently higher than those of both AM and MA over all durations of treatment, and the differences between AM and MA levels were not significant. Interestingly, there was no significant correlation between body weights of the animals at the beginning of the drug treatments and brain levels of AM ($r = +0.098$, $n = 32$; Fig. 2), MA ($r = -0.117$, $n = 32$), or EA ($r = 0.20$, $n = 30$). Residual brain drug levels were consistently higher than levels in the striatum (compare Figs. 6 and 7).

Discussion

Levels of monoamines and their acidic metabolites in vehicle-treated controls were comparable with levels previously determined in this and other laboratories. As has been previously reported (Nwanze and Jonsson 1981; Ellison 1983; Ellison and Ratan 1982; Gately et al. 1987), continuous infusions of AM produced long-lasting depletions of DA and its metabolites (DOPAC and HVA) in the striatum but not in the nucleus accumbens. The striatal depletion of DA was evident after 24 h of treatment and decreased further after 7 days. That these AM-induced depletions are associated with degeneration of DA-releasing terminals has been verified by other researchers using histochemical analyses (Ricaurte et al. 1984). The present finding of DA depletions in the striatum but not nucleus accumbens or olfactory tubercle support previous work (Ellison et al. 1978) indicating that dopaminergic neurotoxicity during or after continuous AM infusions is restricted to the striatum. Interestingly, NA levels in the striatum were also reduced, especially after 7 days of treatment. This may be due to neurotoxicity towards NA terminals projecting to the striatum, a relatively minor input (compare the NA levels between the accumbens and striatum). AM did not affect 5-HT levels in either the striatum or the olfactory tubercles. Levels of 5-HT were consistently increased in the accumbens by AM, but this difference was statistically significant only after 3 days of treatment. This may reflect the relatively weak MAO-A activity of AM (Green and Hait 1980).

Neither MA nor EA produced depletions of any of the three measured monoamine neurotransmitters, as was found with AM in the case of DA and as reported by others for MDMA with regard to 5-HT neurons in rats (Battaglia et al. 1987*a*, 1987*b*, 1988; Commins et al. 1987; Schmidt 1987; Schmidt et al. 1986; Stone et al. 1986, 1988) and primates (Insel et al. 1989; Kleven et al. 1989; Ricaurte et al. 1988*a*, 1988*b*). While chronic MDMA produces a long-term depletion of 5-HT in the striatum, but not the nucleus accumbens (Nash et al. 1990), in a fashion similar to AM's effects on DA, such regionally selective actions of chronically administered ring-substituted methoxy and ethoxy analogues were *not* apparent. A similar lack of neurotoxicity has been reported for 4-methoxyphenylethylamine (Hwang and Van Woert 1979) and 4-methoxytranylcypromine (McKenna et al. 1990), another AM analogue. Neither AM analogue therefore appears to have the same neurotoxic potential as AM, methamphetamine, or MDMA, even though a treatment regimen (continuous infusions for 14

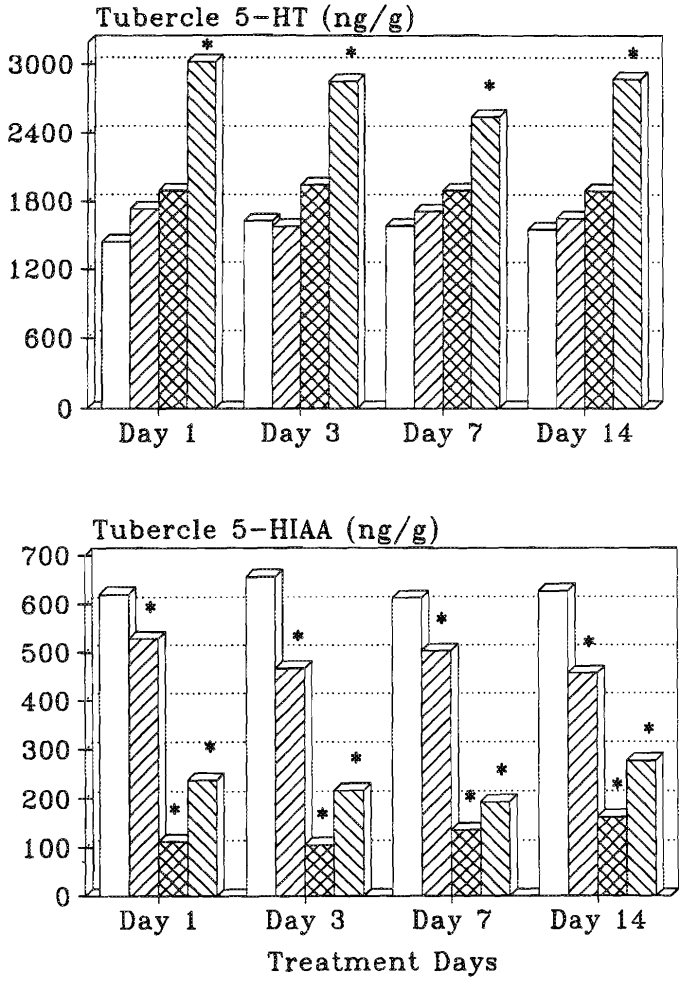

FIG. 5. Levels of serotonin (5-HT) and its metabolite (5-HIAA) in the olfactory tubercle, expressed as a proportion of tissue weight, after different durations of subcutaneous infusions of vehicle (□), AM (▨), MA (▩), or EA (▧) at the dose of 40 μmol/day for each drug. *, significantly different from vehicle, HSD post-hoc test, $p < 0.05$.

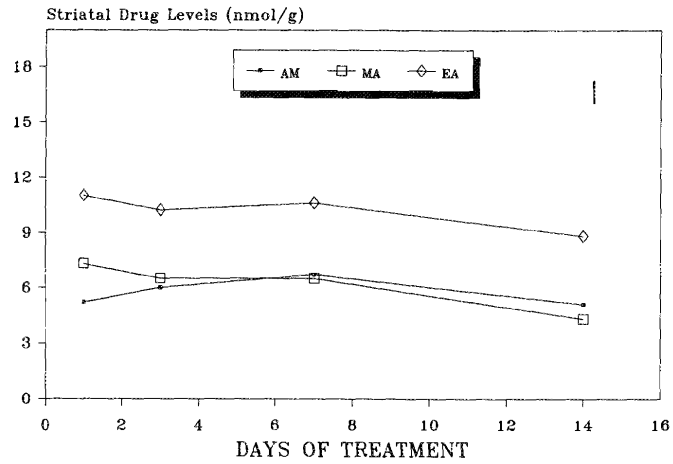

FIG. 6. Drug concentrations (nmol/g tissue) of AM (AMPH), 4-methoxyamphetamine (MA), and 4-ethoxyamphetamine (EA) in striatal tissue after 1, 3, 7, or 14 days of continuous infusions of rats with one of the drugs (40 μmol/day), using osmotic minipumps. Significantly higher levels of 4-ethoxyamphetamine were achieved than for either of the two comparison compounds. The line in the upper right corner represents the standard error, derived from the within subjects error term from the analysis of variance.

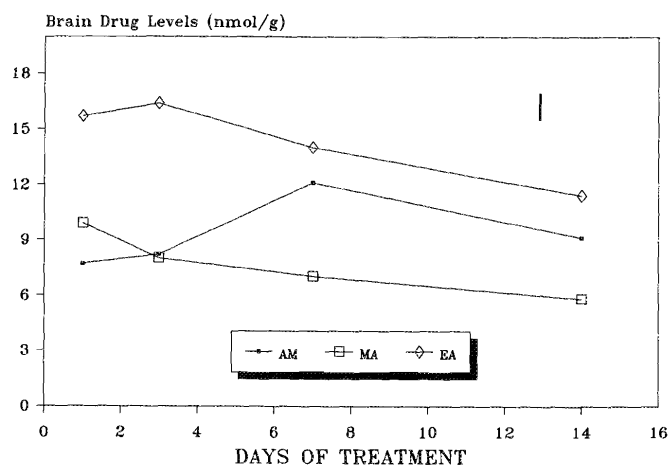

FIG. 7. "Residual" brain (i.e., excluding striatum, nucleus accumbens, and olfactory tubercle) drug concentrations (nmol/g tissue) of AM (AMPH), 4-methoxyamphetamine (MA), and 4-ethoxyamphetamine (EA) after 1, 3, 7, or 14 days of continuous infusions of rats with one of the drugs (40 μmol/day), using osmotic minipumps. Significantly higher levels of 4-ethoxyamphetamine were achieved than for either of the two comparison compounds. There were no significant effects of treatment duration or interactions between drug–treatment duration, indicating that steady-state levels of the drug are reached rapidly, within the 1st day. The line in the upper right corner represents the standard error, derived from the within subjects error term from the analysis of variance.

days) that enhances the neurotoxic effects of AM (Ellison et al. 1978) was followed. Furthermore, the lack of depletions of monoamines cannot be attributed to differences in achieving brain or striatal levels of the analogues, since such levels of MA were found to be the same as for AM and levels of EA were almost twice as high.

Instead, with this regimen, MA yielded increases of DA in the striatum and decreases of its metabolites, with DOPAC being marginally more sensitive to this effect than HVA. In addition, 5-HT levels were increased in the accumbens and 5-HIAA levels were decreased in all areas. This profile indicates potent MAO inhibition, with selectivity for MAO-A, as has been previously reported for MA (Green and Hait 1980), and appears to be more important inside 5-HT neurons than extraneuronally (Ask et al. 1983). Green and Hait (1980) found that MA was over 20 times more potent as an MAO-A inhibitor *in vitro* and 10 times more potent *in vivo* than AM. Ring substituents at the *para* position generally increase selective inhibition of MAO-A, as with MA, 4-hydroxyamphetamine (Arai et al. 1990), 4-hydroxynorephedrine (Arai et al. 1990), and 4-methoxytranylcypromine, a side-chain cyclic analogue of AM (McKenna et al. 1990).

The profile of EA's effects on brain monoamines is similar to that of MA, but not like that of AM. Its effects on 5-HT are greater than those of MA, and this may be due to greater sustained brain levels of EA, and (or) greater intrinsic activity. Other experiments have indicated that acute administration of these drugs does not result in greater brain levels of EA than those of MA or AM, nor does EA produce a greater effect on monoamines when administered acutely (Martin-Iverson et al.

1991). These data, taken together with the present findings, suggest that the presence of an ethoxy group at the *para* position may reduce metabolism of this compound or increase storage in lipophilic tissue, resulting in higher brain levels during chronic administration. If inhibition of metabolism of the AM compound occurs because of blockade of hydroxylation at the *para* position, which occurs to some degree with AM itself (Castagnoli 1978), then one would expect the same levels of MA as EA. However, this was not observed; levels of MA were more similar to those of AM, not to those of EA. Therefore, it is likely that EA levels are sustained at relatively high levels because of less accessibility through metabolism via other routes and (or) increased binding to lipid or protein tissue elements.

Chronic treatment with EA produces effects similar to MAO-A inhibitors, such as clorgyline. Chronic treatment with another AM analogue, tranylcypromine, which is a potent MAO inhibitor, also fails to produce neurotoxic effects (McKenna et al. 1990). The possibility is therefore raised that the toxic effects of other AM compounds with less potent MAO inhibition may actually be mediated by the production of peroxides or free radicals during oxidation by MAO. The more potent MAO inhibitors may block this process, reducing the potential for neurotoxicity. Note that both the present data and this hypothesis are contrary to the view that increased inhibition of MAO would lead to increased metabolism of AM compounds to 6-hydroxydopamine-like toxins via a nonenzymatic route (Seiden and Vosmer 1984). This hypothesis could be tested in the future by examining whether or not co-administration of a potent MAO inhibitor with AM would block the neurotoxic effects of AM.

Striatal and "residual" brain concentrations of the three drugs tested were not significantly altered by duration of treatment, indicating that maximal levels are reached within 24 h. Furthermore, there were no significant correlations between brain drug levels and the weights of the rats at the initiation of treatment. This indicates that giving the drugs in concentrations that are based only on constant delivery per unit time but independent of body weight (i.e., not on a drug $\cdot$ kg^{-1} $\cdot$ day^{-1} basis) is not influenced by variation in body weights, within the range of weights of animals in the present experiments. Levels of EA were significantly higher than those of MA and AM throughout the 14 days of treatment in both striatum and "residual" brain tissues. This may be due to an expected increase in lipophilic properties with the ethoxy substituent, increasing sequestering of the drug in lipophilic tissues. Residual brain levels of all three drugs were higher than the corresponding levels in striatum, and this may be due to greater lipid content of areas such as the hippocampus. This finding is interesting in that it might have been expected to find higher levels of the amphetamines in the striatum if there was uptake of the compounds into dopaminergic terminals, as indicated by the effects on DA and DOPAC levels.

Some evidence suggests that hallucinogens produce their effects via actions on 5-HT neurons, or on cells postsynaptic to 5-HT-releasing terminals, although the specific action that determines hallucinogenic activity has not yet been identified (Jacobs and Trulson 1981). It is apparent from this study that both of the ring-substituted amphetamines have more profound effects on 5-HT than does AM. Since EA is similar to MA in some respects, it seems likely that it may be similar to MA with respect to those (presently unknown) neurochemical actions responsible for hallucinogenic effects. However, as the observed effects are consistent with selective MAO-A inhibition, and this action is not in itself positively correlated with hallucinogenic effects, no definite conclusions on the potential hallucinogenic properties of this compound can be drawn on the basis of the present data.

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