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# A STUDY ON THE ACUTE EFFECT OF AMPHETAMINE ON THE URINARY EXCRETION OF BIOGENIC AMINES AND METABOLITES IN MONKEYS

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**1** The effects of an acute dose (3 mg/kg) of amphetamine on the urinary excretion of phenylethylamine (PEA), *p*-tyramine, their metabolites, catecholamine metabolites and *p*-hydroxymandelic acid, a major metabolite of *p*-octopamine were evaluated in the monkey. Amphetamine excretion was also measured.

**2** Amphetamine was slowly eliminated from the body, being found in the urine at least six days after administration.

**3** Amphetamine increased the excretion of PEA and decreased that of its major metabolite, phenylacetic acid (PAA). This pattern of changes is similar to that previously found in the urine of chronic schizophrenics.

**4** The excretion of the dopamine metabolite, 3,4-dihydroxphenylacetic acid (DOPAC) was markedly reduced, that of vanilmandelic acid (VMA) remained unchanged while 3-methoxy-4-hydroxyphenylglycol (MHPG) was increased on the day of drug administration and persisted for at least a further six days. A similar extended effect on the excretion of *p*-hydroxymandelic acid (it was reduced) was also observed.

**5** The excretion of *p*-tyramine but not its metabolite, *p*-hydroxyphenylacetic acid, was decreased by amphetamine during treatment and returned to normal levels six days later.

**6** From the results obtained, it was concluded that amphetamine effects on behaviour cannot exclusively be attributed to its influence on catecholamines and that other biogenic amines may be involved.

**7** Since PEA elicits many behavioural changes similar to those seen with amphetamine, and since amphetamine increases PEA excretion, we suggest that amphetamine may exert some of its behavioural responses through the release of PEA.

## Introduction

In the experimental animal, amphetamine-induced behavioural abnormalities have been used by some workers as a model of psychotic behaviour in man (Woodrow, Reifman & Wyatt, 1978). Studies employing this model have suggested that schizophrenia may be induced by an endogenous amphetamine-like psychotogen such as phenylethylamine (PEA) (Fischer, Spatz, Heller & Reggiani, 1972). Furthermore, the behavioural and pharmacological responses to PEA and amphetamine are believed to be associated with increased utilization and synthesis of catecholamines (Sabelli & Mosnaim, 1974; Moore, 1977; Roberts & Patrick, 1979). The similar behavioural and pharmacological properties of amphetamine and PEA form the basis of the so called PEA hypothesis of schizophrenia which speculates a disturbance in the disposition of PEA in schizophrenia (Wyatt, 1978). This hypothesis has recently received some support from reports that PEA and its metabolite, phenylacetic acid (PAA), are excreted in greater and smaller amounts, respectively, in the urines of some schizophrenic patients (Wyatt, Potkin, Cannon, Buchsbaum, Murphy, Karoum, Gillin & Stoff, 1978; Potkin, Karoum, Chuang, Cannon-Spoor, Philips & Wyatt, 1979) and that PAA concentration is elevated in the cerebrospinal fluids of schizophrenics (Sandler, Ruthven, Goodwin, King, Pettit, Reynolds, Tyrer, Weller & Hirsch, 1978).

In order to evaluate the suggestion made by Borison, Mosnaim & Sabelli (1975), that PEA mediates some of the behavioural effects of amphetamine and to determine how amphetamine influences the overall body metabolism of PEA and other biogenic amines, we undertook the present study of the effects of short-term administration of amphetamine on the urinary excretion of a number of important biogenic

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amines and their metabolites. These amines include PEA, *p*-tyramine, *p*-octopamine, dopamine and noradrenaline (NA).

## Methods

### *Materials*

Urines were collected from five well adapted chair-restrained rhesus monkeys (*M. mulatta*, 5.5–7.0 kg) as previously described (Perlow, Karoum, Braun & Wyatt, 1979). As a preservative, 10 ml of 10% disodium edetate (EDTA) was added to each 24 h urine collection. Three consecutive 24 h urine collections were obtained from each animal and designated 'First baseline urines'. (+)-Amphetamine sulphate (3 mg/kg, daily) was then administered intramuscularly in divided doses and urine collected for another 24 h. A second set of urines was collected five and six days later and designated 'Second baseline urines'. The urines were stored at −40°C until analyzed.

### *Preparation of samples for analysis*

Phenylethylamine, amphetamine (Karoum, Nasrallah, Potkin, Chuang, Moyer-Schwing, Philips & Wyatt, 1979) and the PEA metabolite, phenylacetic acid (PAA) were measured as previously described for human urine (Martin, Karoum & Wyatt, 1979). Dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), vanilmandelic acid (VMA) and *p*-hydroxymandelic acid were assayed as described for their analysis in cerebrospinal fluid (Karoum, Gillin, Wyatt & Costa, 1975a; Karoum, Gillin & Wyatt, 1975b). In these latter analyses, 0.1 ml of urine was mixed into 1 ml 1 N HCl containing 100 ng of deuterated isomers of each of the metabolites. The metabolites were extracted into ethylacetate and then derivatized to their methylester/pentafluoropropionate derivatives (Karoum *et al.*, 1975a; Perlow *et al.*, 1979).

*p*-Tyramine was measured directly by mixing 10 μl of urine in 20 μl of a solution containing 25 ng of deuterated *p*-tyramine ([$^2H_4$]-tyramine). The mixture was evaporated under a gentle stream of $N_2$ and the *p*-tyramine in the dry residue converted to its pentafluoropropionate derivative (Karoum *et al.*, 1979).

3-Methoxy-4-hydroxyphenylglycol (MHPG) was measured as described previously (Karoum, Moyer-Schwing, Potkin & Wyatt, 1977).

### *Mass fragmentography*

All analyses were carried out by mass fragmentography employing a model 4000 Finnigan gas chromatography quadrupole mass spectrometer (Finnigan Corporation, Sunnyvale, CA). For the analysis of PEA and *p*-tyramine, a 12 ft $\frac{1}{8}$ inch o.d. steel column packed with 0.5% OV-22 + 2% SE54 + 1% OV-210 coated on 80/100 mesh chromosorb W(HP) (Pierce Chemical Company, Rockford, IL.) was used. For all other compounds, we used an 8 ft $\frac{1}{8}$ inch o.d. steel column packed with 3% SE-54 (Analabs, New Haven, CT.). Quantification was achieved by comparing the peak heights of the non-deuterated compounds with those of the appropriate deuterated isomers.

The fragments selected for mass fragmentography are shown in Table 1.

**Table 1** Mass to charge ratio (m/e) of fragments selected for the mass fragmentography of the various biogenic amines and metabolites measured

| *Compound* | *m/e of the non-deuterated compound* | *Structure and m/e of the deuterated isomer* |
|---|---|---|
| Phenylethylamine (PEA) | 104 | [$^2H_4$]-PEA, 107 |
| Phenylacetic acid (PAA) | 268 | [$^2H_7$]-PAA, 275 |
| *p*-Tyramine (Tyr) | 266 | [$^2H_4$]-Tyr, 269 |
| Amphetamine (Amph) | 118 | [$^2H_6$]-Amph, 123 |
| *p*-Hydroxyphenylacetic acid (PHPA) | 312 | [$^2H_2$]-PHPA, 314 |
| *p*-Hydroxymandelic acid (PHMA) | 445 | [$^2H_2$]-PHMA, 447 |
| 3,4-Dihydroxyphenylacetic acid (DOPAC) | 387 | [$^2H_5$]-DOPAC, 392 |
| Homovanillic acid (HVA) | 283 | [$^2H_5$]-HVA, 285 |
| Vanilmandelic acid | 445 | [$^2H_3$]-VMA, 448 |
| 3-Methoxy-4-hydroxy-phenylglycol (MHPG) | 622 | [$^2H_3$]-MHPG, 625 |

**Table 2** Twenty-four hour urine excretion of phenylethylamine (PEA), phenylacetic acid (PAA) and amphetamine (Amph) in monkeys ($n = 5$) after amphetamine administration

| | *Description* | *PEA (μg)* | *PAA (mg)* | *Amph (μg)* |
|---|---|---|---|---|
| | Day one of First baseline | 6.9 ± 3.6 | 64.4 ± 8.0 | 0 |
| | Day two of First baseline | 5.1 ± 2.9 | 65.7 ± 15.5 | 0 |
| | Day three of First baseline | 3.2 ± 1.3 | 44.5 ± 6.1 | 0 |
| (A) | First baselines combined | 5.0 ± 2.6 | 57.3 ± 8.3 | 0 |
| (B) | During amphetamine treatment | 15.6 ± 2.2** | 34.4 ± 6.9* | 447 ± 55 |
| | Day one of Second baseline | 7.8 ± 1.7 | 58.4 ± 8.6 | 32.2 ± 11.4 |
| | Day two of Second baseline | 3.5 ± 0.7 | 69.7 ± 11.1 | 13.6 ± 2.1 |
| (C) | Second baseline combined | 5.6 ± 1.1 | 62.2 ± 10.4 | 33 ± 8 |

Twenty-four hour urines were collected for three consecutive days and designated First baseline. Amphetamine (3 mg/kg) was administered intramuscularly in divided doses and 24 h urine collection commenced immediately after the first injection. Five days after amphetamine treatment, two 24 h consecutive urine collections were made and designated Second baseline.

Results are expressed as mean ± s.e.mean.

*$P < 0.05$ comparing (A) with (B) by paired *t*test; **$P < 0.005$ comparing (A) with (B) by paired *t*test.

## Results

The effects of acute amphetamine treatment on PEA, PAA, and amphetamine excretion are summarized in Table 2. Phenylethylamine excretion was increased by about 3 fold after amphetamine ($P < 0.005$) while PAA excretion was reduced ($P < 0.05$). Although amphetamine remained detectable in urines collected six days after amphetamine, the second baseline urines showed normal levels for both PEA and PAA.

Amphetamine reduced the excretion of *p*-tyramine ($P < 0.05$) without altering the excretion of its metabolite, *p*-hydroxphenylacetic acid (Table 3). The excretion of *p*-hydroxymandelic acid, a major metabolite of *p*-octopamine, on the other hand showed a small but consistent tendency towards low levels for the duration of the observation period (Table 3). Thus, although amphetamine lowered *p*-hydroxymandelic acid excretion one day after treatment, this reduction became significant ($P < 0.05$) only in the Second baseline urines.

While the excretion of VMA remained unchanged, MHPG excretion increased during amphetamine administration, and continued to increase during the following six days (Table 4). In contrast to the mixed response seen with the noradrenaline metabolites, the excretion rates of both dopamine metabolites (DOPAC and HVA) decreased in response to amphetamine. Homovanillic acid and DOPAC excretion on the day of drug administration were respectively 59% and 30% of their First baseline values (Table 4). This response was observed only during amphetamine administration.

## Discussion

Except for PEA, it is difficult to determine how the

**Table 3** Urinary daily excretion of *p*-tyramine, *p*-hydroxyphenylacetic acid and *p*-hydroxymandelic acid in monkeys ($n = 5$) after amphetamine administration[a]

| | *Description* | p-*Tyramine acid (μg)* | p-*Hydroxyphenylacetic acid (μg)* | p-*Hydroxymandelic acid (μg)* |
|---|---|---|---|---|
| | Day one of First baseline | 673 ± 127 | 946 ± 108 | 486 ± 44 |
| | Day two of First baseline | 570 ± 41 | 617 ± 140 | 407 ± 63 |
| | Day three of First baseline | 523 ± 56 | 569 ± 166 | 345 ± 38 |
| (A) | First baseline combined | 581 ± 59 | 710 ± 123 | 413 ± 42 |
| (B) | During amphetamine treatment | 285 ± 73* | 603 ± 164 | 376 ± 71 |
| | Day one of Second baseline | 539 ± 101 | 713 ± 64 | 333 ± 72 |
| | Day two of Second baseline | 556 ± 93 | 493 ± 118 | 311 ± 41 |
| (C) | Second baseline combined | 547 ± 89 | 603 ± 83 | 322 ± 23* |

[a] See legend of Table 2 for description of urine collection and amphetamine dosage.

*$P < 0.05$ comparing (A) with (B) or (C) by paired *t*test.

**Table 4** Urinary daily excretion of catecholamine metabolites in monkeys ($n = 5$) after amphetamine administration[a]

| | *Description* | *VMA (μg)* | *MHPG (μg)* | *HVA (μg)* | *DOPAC (μg)* |
|---|---|---|---|---|---|
| | Day one of First baseline | 43.1 ± 7.4 | 341.7 ± 16.9 | 0.91 ± 0.45 | 1.20 ± 0.33 |
| | Day two of First baseline | 53.3 ± 10.2 | 326.1 ± 23.8 | 1.58 ± 0.61 | 1.41 ± 0.75 |
| | Day three of First baseline | 78.6 ± 19.3 | 392.6 ± 13.2 | 1.45 ± 0.6 | 1.15 ± 0.26 |
| (A) | First baseline combined | 58 ± 8 | 353 ± 10 | 1.3 ± 0.5 | 1.25 ± 0.33 |
| (B) | During amphetamine treatment | 48 ± 8 | 589 ± 50* | 0.9 ± 0.1 | 0.38 ± 0.2* |
| | Day one of Second baseline | 99.1 ± 22.6 | 844.6 ± 91 | 2.65 ± 1.2 | 2.5 ± 1.9 |
| | Day two of Second baseline | 85.5 ± 18.1 | 912.5 ± 70 | 1.14 ± 0.26 | 0.75 ± 0.34 |
| (C) | Second baseline combined | 90 ± 18 | 878 ± 39** | 1.9 ± 0.7 | 1.63 ± 1.12 |

VMA = vanilmandelic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; DOPAC = 3,4-dihydroxyphenylacetic acid.

[a] See legend of Table 2 for description of urine collection and amphetamine dosage.

*$P < 0.05$ and **$P < 0.005$ comparing (A) with (B) or (C) by paired $t$ test.

excretions of the other compounds, measured after amphetamine treatment, reflect central responses. Nevertheless, these changes offer an insight into the mechanisms mediating the interaction between amphetamine and the five biogenic amines studied (PEA, *p*-tyramine, *p*-octopamine, dopamine and NA); mechanisms that could equally operate in the periphery and in the brain. Furthermore, since PEA can easily cross the blood brain barrier (Nakajima, Kakimoto & Sano, 1964; Oldendorf, 1971; Philips, Davis, Durden & Boulton, 1975) it is anticipated that its increased peripheral production may parallel a similar elevation in brain PEA. Amphetamine was found to increase brain PEA concentration in rabbits (Borison *et al.*, 1975) and rats (unpublished observation). Increased brain PEA in response to amphetamine treatment can alter the disposition of those central biogenic amines known to interact with PEA (Silkaitis & Mosnaim, 1976; Mosnaim & Wolf, 1978). Indeed, such an interaction can precipitate some of the central effects of amphetamine (Fuxe, Grobecker & Johnson, 1967; Silkaitis & Mosnaim, 1976).

The urinary excretion of some non-catecholic amines and their metabolites are considered by some workers to originate in the gut from dietary products (Perry, Hestrim, McDougall & Hansen, 1966; Seakins, 1971). Others disagree with this assumption (DeQuattro & Sjoerdsma, 1967; Karoum *et al.*, 1979; Martin *et al.*, 1979). The monkeys we used were on the same diet throughout the experiment and as far as we can judge qualitatively, their food consumption remained unchanged. Furthermore, the observed changes after amphetamine treatment cannot be attributed to the stress of handling during drug administration. This is because the monkeys were chair restrained and it took only a few seconds to inject amphetamine. During this time, the monkeys exhibited no overt stressful signs. In addition, as has been previously reported, stress markedly increased the urinary output of catecholamine metabolites in monkeys (Perlow *et al.*, 1979); an effect which we did not find after amphetamine treatment. Thus, while MHPG excretion increased, VMA, HVA and DOPAC excretion decreased (Table 4). The increase in MHPG excretion after amphetamine cannot be attributed to stress because it remained elevated in the Second baseline urine (Table 4). Therefore, we believe that the changes observed in the urinary excretion of the amines and metabolites (Table 1–4) after amphetamine are probably not related to the diet or the amount of food consumed, nor to the effects of handling.

The exact mechanism of action of amphetamine on behaviour is only partially understood but appears to involve more than one neurotransmitter system. We have demonstrated that amphetamine also influences the urinary excretion of PEA and *p*-tyramine as well as the metabolites derived from PEA, *p*-octopamine, NA and dopamine (Tables 2–4). Whether or not these changes are peripherally or centrally derived, has yet to be determined. However, some similarities exist between the effects of the acute amphetamine treatment observed here and those described in the brain. Thus, besides its effect on brain PEA as discussed earlier, amphetamine was reported to reduce straital concentration of *p*-tyramine (Juroio & Danielson, 1978) and to reduce the metabolism of dopamine in certain brain areas (Speciale, Karoum & Wyatt, 1980). These changes are similar to those found in this study (Tables 3 and 4).

Our study provides some information on the long-term effects of acute amphetamine treatment on biogenic amines. As shown in Tables 3 and 4, *p*-octopamine metabolism, as manifested by a reduction in *p*-hydroxymandelic acid (Table 3) and NA metabolism as manifested by an increase in MHPG excretion (Table 4) persisted and in fact became

more pronounced over the five day observation period. From this experiment, we do not know how long these changes would have lasted or if they were related to the persistent low levels of amphetamine that continued to be detected in the urine long after treatment was terminated (Table 2). A similar extended response to short-term administration of amphetamine has been seen in other systems after the termination of chronic amphetamine treatment (Ellison, Eison, Huberman & Daniel, 1978; Trulson & Jacobs, 1979; Fuller & Hemrick-Leucke, 1980). This phenomenon of extended amphetamine effect warrants further study because of its possible implication in the clinical abuse of this drug.

The report by Fischer *et al.* (1972) that PEA excretion is elevated in some schizophrenics was recently confirmed in paranoid schizophrenia (Potkin *et al.*, 1979). The involvement of PEA in the aetiology of schizophrenia is further suggested from a report of elevated PAA excretion in the cerebrospinal fluid of some schizophrenic patients, a phenomenon attributed to increased PEA metabolism (Sandler *et al.*, 1978). In addition, we have observed a reduction in PAA excretion in schizophrenia (Wyatt *et al.*, 1978) an effect which apparently is not associated with a decrease in total body A and B type monoamine oxidase activity, but seems to be related to an alteration in phenylalanine transamination to phenylpyruvic acid (unpublished). Phenylpyruvic acid is the major precursor of urine PAA (Curtius, Vollmin & Baerlocher, 1972; additional relevant information is unpublished). Thus it appears that while cerebrospinal fluid offers an index to changes in central PEA metabolism, urine PAA excretion is of limited diagnostic value. The picture of an elevated PEA and reduced PAA urinary excretion observed in schizophrenia is similar to the changes found in monkeys after amphetamine sulphate (3 mg/kg, daily). However, the importance of this latter correlation between man and monkeys cannot be evaluated critically because amphetamine was administered over one day to the monkeys, while all of the patients studied were chronically ill.

Our results agree with the earlier observation of Borison *et al.* (1975) and Sabelli & Borison (1976) that amphetamine increases the release of PEA. Although the methods employed by these workers are believed to lack specificity, we were recently able to detect a significant elevation in rat brain PEA concentration after amphetamine administration (unpublished) using mass fragmentography. In that PEA produces the same behavioural responses as amphetamine, and like amphetamine, stimulates the release of central catecholamines (Perlow, Chiueh, Lake & Wyatt, 1980), it is possible that amphetamine may act indirectly on catecholamines via its ability to release PEA. If this is correct, the panoply of metabolite changes seen here in response to amphetamine should, at least in part, be reproduced by PEA. In a recent publication (Tinklenberg, Gillin, Murphy, Staub & Wyatt, 1979), PEA behavioural effects in the rhesus monkey were reported to be blocked by pretreatment with α-methyl-*p*-tyrosine; a blockade similar to that observed with amphetamine (Aceto, Harris, Lesher, Pearl & Brown, 1967; Sulser, Owens, Norvich & Dingell, 1968). Another possibility which may lead to increased PEA excretion by amphetamine, is related to α-demethylation of amphetamine to PEA; as will be shown elsewhere this latter conversion is biologically impossible.

The reduction in the excretion of *p*-tyramine, *p*-hydroxymandelic acid, DOPAC and PAA cannot be attributed to inhibition of monoamine oxidase because the excretion of other deaminated metabolites was either not changed (*p*-hydroxyphenylacetic acid, HVA and VMA) or increased (MHPG) (Table 3, 4). Thus at the dose employed, the changes observed in the excretion of the amines and metabolites cannot wholly be associated with monoamine oxidase (MAO) inhibition. Although some inhibition of MAO cannot be ruled out, we believe that most of the changes induced by amphetamine are associated with other mechanisms. These mechanisms may include changes in the amines synthesis, their release and metabolism through reduced neuronal firing rates.

While the decrease in dopamine metabolites excretion can be explained in terms of reduced peripheral and central dopaminergic neuronal firing rates (Bunney, Walters, Roth & Aghajanian, 1973; Bunney & Aghajanian, 1977), and in terms of increased release and reduced amine uptake (Besson, Cheramy, Feltz & Glowinski, 1971; Ross, 1978); the reduction in *p*-tyramine excretion is probably associated with a reduction in *p*-hydroxylation of PEA to *p*-tyramine as a result of the metabolism of amphetamine. Amphetamine is primary metabolized by hydroxylation (Axelrod, 1954; Goldstein & Anagnoste, 1965; Williams, 1967); a phenomenon which may competitively inhibit *p*-hydroxylation of PEA to *p*-tyramine. Increased PEA excretion following the administration of either PEA or pargyline to man is accompanied by a concomitant increase in *p*-tyramine excretion (Karoum, Potkin, Murphy & Wyatt, 1978) presumably via the *p*-hydroxylation of PEA. The failure of *p*-tyramine excretion to parallel the increase in PEA excretion after amphetamine may therefore correspond to a reduction in PEA *p*-hydroxylation pathway to *p*-tyramine (Silkaitis & Mosnaim, 1976; Mosnaim & Wolf, 1978).

The increase in MHPG observed after amphetamine is interesting because of its bearing on MHPG excretion in emotionally depressed humans. Depressed patients who responded to amphetamine

with elevation of mood were reported to show either no change or a slight increase in their urine MHPG, while patients who failed to respond, showed marked decrement in urine MHPG (Fawcett, Maas & Dekirmenjian, 1972; Maas, 1978). As shown in Table 4, amphetamine significantly increased MHPG; an increase which continued to grow for at least six days. This tendency towards increased MHPG excretion was also observed by Angrist, Shopsin & Gershon, 1972, in three amphetamine abusers.

In conclusion, from the various changes in the excretion of biogenic amines and their metabolites that were observed in the monkey, it appears that the biochemical and behavioural effects of amphetamine can no longer be considered to be limited to just the catecholamines. Furthermore, the ability of amphetamine to produce changes in PEA and PAA excretion similar to those found in chronic schizophrenia, coupled with the fact that both PEA and amphetamine induce almost identical behavioural responses in the experimental animal, suggest that PEA may be involved in mediating some of the behavioural and biochemical effects of amphetamine.

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