

Norephedrine as Metabolites of [¹⁴C]Amphetamine in Urine in Man

By J. CALDWELL, L. G. DRING and R. T. WILLIAMS

Department of Biochemistry, St. Mary's Hospital Medical School, London W.2, U.K.

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(±)-[¹⁴C]Amphetamine sulphate (20mg) was administered orally to each of two human male subjects, and 80–85% of the ¹⁴C was excreted in the urine in 2 days. The metabolites in the first day's urine were examined quantitatively. Apart from the metabolites previously described (Dring *et al.*, 1970), norephedrine (2.2 and 2.6% of dose in the two subjects respectively) and 4-hydroxynorephedrine (0.3 and 0.4% of dose in the two subjects respectively) were also found.

In a previous paper (Dring *et al.*, 1970), the nature of the metabolites of amphetamine in the urine in man and six other mammalian species was examined. In that study the main point of interest was the species difference in the amounts of the major metabolites of amphetamine that were formed and excreted. The occurrence of the so-called false neurotransmitter 4-hydroxynorephedrine [2-amino-1-(4'-hydroxyphenyl)propan-1-ol] and the closely related compound, norephedrine (2-amino-1-phenylpropan-1-ol) as metabolites of amphetamine in the urine of man was not examined in detail, although both were found as minor metabolites in urine of the rat. In the guinea pig norephedrine and in the rat 4-hydroxynorephedrine have been briefly reported as substantial metabolites of methamphetamine (2-methylamino-1-phenylpropane) (Caldwell *et al.*, 1971*a,b*) and both of these compounds have been found as minor metabolites of this drug in the urine of two male volunteers, whose informed consent was obtained (Caldwell *et al.*, 1972). We now report quantitative results on the occurrence of norephedrine and its 4-hydroxy derivative in the urine of the same two human subjects receiving [¹⁴C]amphetamine sulphate.

Materials and Methods

[¹⁴C]Amphetamine sulphate {(±)-2-amino-1-phenyl[1-¹⁴C]propane; 20mg; 3 μCi} was taken orally dissolved in water by two male subjects, C and D, and their urine was collected daily for 48 h. The output of ¹⁴C was measured by liquid scintillation counting for radioactivity with a Packard Tri-Carb model 3320 scintillation spectrometer (see Bridges *et al.*, 1967). 4-Hydroxyamphetamine [2-amino-1-(4'-hydroxyphenyl)propane], benzyl methyl ketone (1-phenyl-

propan-2-one) and benzoic acid were determined by isotope dilution as described by Dring *et al.* (1970) and norephedrine and 4-hydroxynorephedrine as described by Caldwell *et al.* (1972). Amphetamine was determined after extraction from urine made alkaline (pH 14) as described by Caldwell *et al.* (1972) for methamphetamine. It was identified by its *R_F* on t.l.c. in two solvent systems as described by Caldwell *et al.* (1972).

Results and Discussion

The output of ¹⁴C in 2 days after an oral dose of (±)-amphetamine sulphate (20mg) and the amounts of the metabolites in the urine of the first day after dosing are shown in Table 1. The outputs of ¹⁴C and of amphetamine, 4-hydroxyamphetamine, benzoic acid and benzyl methyl ketone in the two subjects are similar to those found in the three subjects examined by Dring *et al.* (1970).

Both norephedrine and 4-hydroxynorephedrine were found in the urine, the former amounting to just over 2% of the dose and the latter to about 0.4%. 4-Hydroxynorephedrine has been detected qualitatively by Cavanaugh *et al.* (1970) as a metabolite of amphetamine in the urine of man, but norephedrine has not been previously reported. False neurotransmitters have been suggested as being responsible for the partial adrenergic blockade seen after chronic amphetamine administration (Gill *et al.*, 1967; Cavanaugh *et al.*, 1970) and as being the cause of tolerance to amphetamine (Brodie *et al.*, 1970). Whether this is in any way related to the abuse of these drugs is open to conjecture, but it is noteworthy that the subjects investigated here produce five to ten times as much 4-hydroxynorephedrine from methamphetamine as from amphetamine (Caldwell *et*

Table 1. *Metabolites of amphetamine in the urine of two human subjects*

[¹⁴C]Amphetamine sulphate (20 mg; 3 μ Ci) was taken orally in water by two male human subjects, C and D. Each subject weighed 70 kg and the dose of the drug was about 0.29 mg/kg. Urine was collected daily and analysed as described in the text.

¹⁴ C found in urine		% of dose	
Subject	...	C	D
Day 1	...	56.9	63.6
Day 2	...	24.5	21.1
Total	...	81.4	84.7

Metabolite found in urine of day 1		% of dose	
Amphetamine		18.0	20.0
4-Hydroxyamphetamine (total)*		2.4	4.4
Norephedrine		2.2	2.6
4-Hydroxynorephedrine (total)*		0.3	0.4
Benzyl methyl ketone†		0.9	1.7
Benzoic acid (total)*		28.2	27.1
Sum of metabolites		52.0	56.2

* Free and conjugated compound were measured together.

† Benzyl methyl ketone did not occur in the urine as such, but was formed on acid hydrolysis (see Dring *et al.*, 1970).

al., 1972), which may perhaps be related to the greater dangers of methamphetamine to abusers (Leak, 1958; Kramer *et al.*, 1967; O'Connor, 1968).

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