consistently lower than their arterial counterparts, the estimated amount eliminated will then be smaller and result in a larger estimated amount of drug remaining in the body. This will be the case even at the attainment of the steady state as shown in Fig. 1a. As a result, estimated V_{ss} values from venous data are higher than from arterial data. The dotted lines in Fig. 1a, would be obtained if the infusion continued to the steady state.

From a physiological point of view, the driving force for drug distribution and elimination lies mainly in the arterial blood (Chiou 1981, 1982a; Chiou & Lam 1982; Chiou et al 1981), hence the use of arterial plasma data is more appropriate to describe the disposition kinetics of drugs. The results of the present study have demonstrated the uptake and release of procainamide by the leg (assumed to be a non-eliminating tissue) during infusion and post-infusion periods, respectively. V_{ss} determination from arterial plasma, therefore, better reflects the 'true' apparent distribution volume of procainamide in these rabbits. The inclusion of an additional non-eliminating tissue from a venous sampling site simply increases this volume term by a factor of 1·5. Similar magnitudes of difference due to the use of arterial or venous plasma data in the determination of the V_{ss} of propranolol in dogs and rabbits have also been recently reported (Lam & Chiou 1981).

In the light of the potential effect of the A–V difference on the determination of V_{ss} and the difficulty and risk involved in sampling the systemic arterial blood, new equations employing venous plasma and urinary excretion data have been recently proposed for V_{ss} determination (Chiou & Lam 1981; Chiou 1982a). In other words, the determination of V_{ss} using these new equations is theoretically independent of the source of blood or plasma employed.

Finally, the observed A–V differences are not unique in this study; they have been reported for many compounds in animal and human (Chiou et al 1981; Orskov & Christensen 1969; Slot 1965; Tucker & Mather 1979). Their implications in the determination and in the physiological significance of the apparent volume of distribution at the pseudo-distribution equilibrium (Chiou 1981), and the total body clearance (Chiou 1982b) have been recently discussed.

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Cocaine-induced release of noradrenaline in rat tail artery

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The ability of cocaine to potentiate contractile responses to nerve stimulation and to exogenous noradrenaline has been demonstrated in isolated blood vessel preparations (see Vanhoutte et al 1981 for review). The mechanism of this potentiation is generally believed to involve inhibition of the neuronal uptake process resulting in an increase in the effective concentration of noradrenaline in the vicinity of the adrenoceptors.

Recently, we observed that isolated strips of rat tail artery contract in response to increasing concentrations of cocaine (Webb et al 1980). These contractions were blocked by phentolamine and were reduced after acute adrenergic denervation with 6-hydroxydopamine, suggesting that cocaine causes release of noradrenaline from adrenergic nerve endings. The present experiments were designed to test this interpretation.

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Adult, male albino rats (Sprague-Dawley, 350–400 g) were killed by cervical dislocation and tail arteries isolated, stored in physiological salt solution (PSS), and cut helically into strips (1·0 mm × 10 cm) under a dissecting microscope. After dissection, the preparations were incubated for 4 h in PSS containing 3×10^{-7} M [7-^{3}H] noradrenaline (spec. act. = 8·8 Ci mmol^{-1}; Amersham/Searle, Arlington Heights, IL). At the end of the incubation period, the strips were rinsed in fresh PSS and mounted for superfusion as described previously (Vanhoutte et al 1973; Lorenz & Vanhoutte 1975).

The arterial strips were suspended in a moist tunnel-shaped chamber maintained at 37 °C. The preparations were superfused at 3 ml min^{-1} by a constant flow roller pump with PSS. A three-way stopcock, upstream from the pump, allowed rapid switching from control solution to a

solution containing 10^{-4} M cocaine. The preparations were connected to a strain gauge for isometric tension recording. The initial tension was set at 2 g. After this initial stretch, the tension decreased and stabilized within 30 min. At this time, sampling of the superfusate was started. The superfusate was collected at 2 min intervals for direct estimation of total radioactivity. During selected 5 min periods, the superfusate was collected for subsequent chromatographic analysis.

Tritiated noradrenaline was separated from its major metabolites [3,4-hydroxymandelic acid (DOMA), 3,4-dihydroxyphenylglycol (DOPEG), 3-methoxy-4-hydroxyphenylglycol (MOPEG), normetanephrine (NMN), and 3-methoxy-4-hydroxy-mandelic acid (VMA)] by a chromatographic method as described by Verbeuren et al (1977).

Samples (1 ml) of the superfusate and of the fractions obtained during the chromatographic procedure were added to 10 ml of Insta-gel (Packard Instrument Corp.), and the radioactivity was measured in a liquid scintillation counter (Packard, model 3330). The samples were counted for 10 min. Corrections for quenching were made by the external standard method. The counting efficiency was 42 per cent.

Five rat tail arteries, previously incubated in a solution containing 3×10^{-7} M [^{3}H]noradrenaline, were studied in the superfusion apparatus (Fig. 1). Treatment with 10^{-4} M cocaine caused an increase in tension (from 1·71 ± 0·14 g to 1·87 ± 0·11 g; a 30–40% change in force compared to a maximal response induced by exogenous noradrenaline) and in total radioactivity of the superfusate (Fig. 1). The increase in total radioactivity was due to an increase in [^{3}H]noradrenaline (199 ± 18% of control), DOPEG (161 ± 21%), DOMA (137 ± 23%) and non-catechol metabolites (MOPEG = 110 ± 7%; VMA = 136 ± 28%). The effects of cocaine were reversible.

The current experiments demonstrate that administration of 10^{-4} M cocaine to the rat tail artery strips produces a contraction which is paralleled by an increase in [^{3}H]noradrenaline in the superfusate. Additionally, there was a large

Table 1. Cocaine-induced release of noradrenaline (NA).

Isolated tissue prepn and concn of cocaine	Parameters	Results	Ref.
Strips of rat vas deferens 10^{-5} M	Overflow of ^{3}H-NA and metabolites	1. No change in efflux of total radioactivity 2. Overflow of ^{3}H-NA increased by 10% 3. Overflow of DOPEG decreased by 16% 4. Overflow of DOMA increased by 67%	Graefe et al (1973)
Perfused cat spleen 3×10^{-7} to 1×10^{-4} M	Overflow of ^{3}H-NA and metabolites	1. No change in efflux of total radioactivity 2. Overflow of ^{3}H-NA increased by 100–125% 3. No change in metabolites	Cubeddu et al (1974)
Strips of guinea-pig atria 0·03 to 10·0 μg ml^{-1}	Changes in the rate of beating (pacemaker activity)	1. Cocaine caused a concentration-dependent increase in the spontaneous rate of beating 2. The accelerating effect was absent in atria from denervated animals. Thus, cocaine induced the release of NE	Trendelenburg (1968)
Strips of rat tail artery 10^{-4} M	1. Overflow of ^{3}H-NA and metabolites 2. Changes in tension	1. Overflow of total radioactivity increased by 30% 2. Overflow of ^{3}H-NA increased by 99% 3. Overflow of DOPEG increased by 61% 4. Overflow of DOMA increased by 37% 5. Overflow of non-catechol metabolites increased by 19% 6. Tension increased	Current study

increase in the overflow of DOPEG; this metabolite originates mainly from intraneuronal deamination of noradrenaline (see Vanhoutte 1978; Vanhoutte et al 1981). Similar alterations in the basal overflow of [^{3}H]noradrenaline and its metabolites have been observed in adrenergically innervated blood vessels with indirect sympathomimetic amines and agents causing increased leakage of noradrenaline from its storage sites (Muldoon et al 1976, 1977; Verhaeghe et al 1977; Vanhoutte 1978). Our experiments demonstrate that cocaine can augment the leakage or cause displacement of noradrenaline from adrenergic nerve endings in the blood vessel wall, as it does in other adrenergically innervated organs (see Table 1; Trendelenburg 1968; Graefe et al 1973; Cubeddu et al 1974).

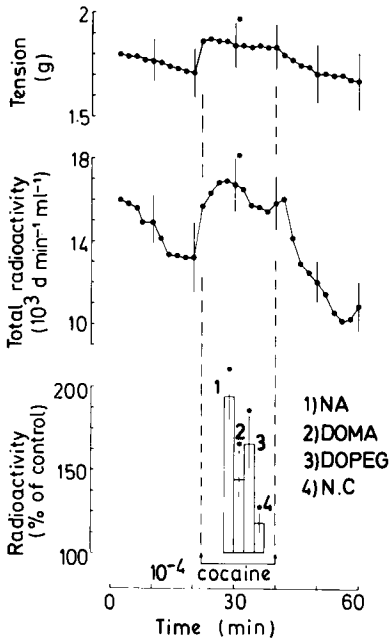

FIG. 1. Effects of cocaine on tail artery strips. Treatment with 10^{-4} M cocaine caused a significant increase in tension (upper panel) and in total radioactivity of the superfusate (middle panel). The increase in total radioactivity was due to an increase in [^{3}H]noradrenaline (NA), DOPEG, DOMA and non-catechol metabolites (lower panel). The asterisks indicate a statistically significant difference between the treated and untreated condition (paired t-test; $P < 0.05$).

The concentration of cocaine used in the present study has frequently been utilized to inhibit neuronal uptake in isolated blood vessels (Furchgott et al 1963; Bevan & Verity 1967; Torok & Bevan 1971; Sullivan & Sparks 1979; Whall et al 1980). Earlier work has shown that lower concentrations (10^{-7} to 10^{-5} M) of the agent also cause contractions which are abolished by α-adrenoceptor blockade and chemical sympathectomy (Webb & Vanhoutte 1979; Webb et al 1980). The present study has important implications concerning the interpretation of results based on the use of cocaine as a 'specific inhibitor' of neuronal uptake in isolated blood vessels.

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