Enhancement of H^3-Norepinephrine Accumulation in Rat Vas Deferens by Cocaine, Imipramine, and Desmethylimipramine

The potentiation of peripheral effects of norepinephrine by cocaine has been well documented. The extensive literature concerning the mechanism of cocaine-induced supersensitivity has recently been reviewed[1,2].

A few years ago, imipramine has also been shown to potentiate the peripheral effects of norepinephrine[3]. This property was demonstrated later for other antidepressant drugs chemically related to imipramine[4-6]. A number of isolated organs have also been used to study cocaine-induced[7-10] and/or imipramine-induced[5-12] supersensitivity to norepinephrine.

It is well known, on the other hand, that both cocaine and imipramine, or imipramine-like compounds, inhibit the uptake of norepinephrine by sympathetic nerve endings in many organs. These uptake experiments have been made by injecting norepinephrine to the animals or more frequently by adding norepinephrine to an isolated organ bath or to a perfusion medium. A comprehensive survey of the literature has been given by IVERSEN[13].

The uptake of circulating norepinephrine at sympathetic nerve endings appears to be the mechanism by which the effects of the transmitter are terminated. Hence blockade of this uptake probably accounts in part for the potentiating effects shown by these compounds on circulatory system or on adrenergically innervated isolated organs.

The inhibition of H^3-norepinephrine uptake by imipramine, desipramine, cocaine, guanethidine, and metaraminol in the isolated heart has been described[14-16]. Some of these substances produce a similar effect on the heart in vivo[17-22]. On the contrary, the influence of such drugs on the uptake of norepinephrine in the vas deferens has been poorly understood although this preparation is widely used to study the effects of drugs on the norepinephrine-induced contraction of this muscle. In a very recent report, however, HÄGGENDAL and HAMBERGER[23] observed an inhibition of norepinephrine uptake by desipramine in the isolated vas deferens of the reserpinized rat, and IVERSEN[24] observed a similar effect by incubating slices of rat vas deferens with H^3-norepinephrine in presence of desipramine, cocaine or metaraminol.

It will be shown, however, that cocaine, imipramine, and desmethylimipramine enhance the norepinephrine accumulation in the rat vas deferens in vivo while inhibiting it in the heart of the same animal.

Methods. Male albino rats (180–230 g) were treated with various substances known to produce supersensitivity to norepinephrine and to reduce uptake or accumulation of exogenously administered norepinephrine in the heart. 2 h later, they received an i.v. injection of DL-norepinephrine-7-H^3 hydrochloride (3680 mc/mM; The Radiochemical Centre, Amersham, England) at a dose of 360 μc/ml/kg body weight. The animals were killed 1 h later. Heart and both vasa deferentia were quickly removed, homogenized with 10% trichloroacetic acid (TCA). H^3-norepinephrine was estimated after isolation of the catecholamines from TCA extracts by alumina adsorption at pH 8.4 and subsequent elution with 0.25 N HCl, according to the method of VON EULER and ORWÉN[25]. All reagents contained 0.01% EDTA (Complexon III, Siegfried). Radioactivity was determined in duplicate experiments, with 0.2 ml extract, 2.0 ml ethanol, 1.5 ml methanol, and 10 ml butyl-PBD scintillator (Scintillator CIBA) solution (0.6% in toluene). All samples were counted in a Packard-Tri-Carb liquid scintillation spectrometer together with H^3-standards. The estimation of catecholamines was carried out essentially by the method of VON EULER and LISHAJKO[26] except that 10 N NaOH was used rather than 5 N NaOH[27]. Results are expressed in terms of norepinephrine.

Results. The effects of a single dose of cocaine (20 mg/kg, s.c.), imipramine (10 mg/kg, orally), desmethylimipramine (6 mg/kg, orally), guanethidine (10 mg/kg, s.c.), L-metaraminol (0.3 mg/kg, s.c.), or reserpine (0.3 mg/kg, s.c.) on the accumulation of H^3-norepinephrine in the rat heart and vas deferens are shown in the Figure. In the heart, these compounds produced a strong reduction of H^3-norepinephrine accumulation. In the same animals, reserpine or L-metaraminol did not inhibit significantly H^3-norepinephrine accumulation in the vas deferens. Surprisingly, cocaine, imipramine, desmethylimipramine, or guanethidine even enhanced H^3-norepinephrine accumulation. There was a borderline increase for guanethidine but cocaine, imipramine and desmethylimipramine had increased the accumulation by 57.7, 80.2 and 94.7%, respectively.

The Table shows the effects of these drugs on the norepinephrine content of heart and vas deferens under the

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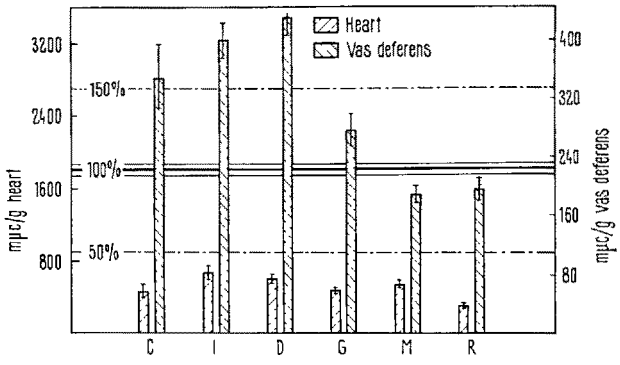
conditions used to determine norepinephrine accumulation. It is particularly interesting to note the lack of depleting action of L-metaraminol on the vas deferens at a time where cardiac stores have lost 60–70% of their norepinephrine content. Similarly the depleting action of reserpine was less in the vas deferens than in the heart.

Discussion. Cocaine, imipramine, and desmethylimipramine potentiate the pharmacological actions of norepinephrine on heart or on isolated vas deferens. This was explained by the ability of this type of substance to inhibit the uptake of the amine by sympathetic nerve endings[13]. In the experiments described above the inhibition of amine uptake has been demonstrated to occur in cardiac tissue and this is in agreement with previous reports of other investigators using similar procedures (for references see [13]). Since cocaine, imipramine, and desmethylimipramine potentiate the smooth muscle stimulant action of norepinephrine also in the isolated vas deferens, the enhanced norepinephrine accumulation in this organ was quite unexpected. The explanation of the mechanism by which the H^3-norepinephrine accumulation is enhanced in the vas deferens needs further study because the present experimental situation does not allow to decide whether the enhancement of H^3-norepinephrine accumulation is due to an increased net uptake or to an increased exchange of H^3-norepinephrine with endogenous amine stores. Hitherto, 2 examples of enhanced H^3-norepinephrine accumulation have been reported in the vas deferens: (1) in rats after pretreatment with metanephrine, normetanephrine, or 3-methoxy-4-hydroxyphenylethylamine[28], (2) in immunosympathectomized rats or mice[29–31].

It must be kept in mind that the general behaviour of catecholamines in the vas deferens contrasts with that in other adrenergically innervated organs, such as heart, spleen, or salivary glands, e.g. the norepinephrine content of the rat vas deferens is lowered less, or less rapidly, by reserpine than the norepinephrine stores of the myocardium (see Table); the norepinephrine persists in the vas deferens after hypogastric denervation[32]; the absolute amounts of norepinephrine taken up by the vas deferens is relatively low as compared with its exceptionally rich adrenergic innervation. All these differences might be connected with the particular anatomical pattern of adrenergic innervation of the vas deferens which is characterized by short adrenergic neurons[32]. This factor might have been of importance in the effects described above.

Since the accumulation of norepinephrine also depends on the flow rate[33,34], the possibility has to be taken into account that the effects of the injected norepinephrine as well as those of the norepinephrine resulting from defective uptake in other tissues have been potentiated by cocaine, imipramine, or desmethylimipramine in such a manner as to alter the blood supply to the vas deferens. The norepinephrine-induced redistribution of blood flow, indeed, has been shown to differ qualitatively and quantitatively from one vascular bed to another, in the unanaesthetized rat[35].

Résumé. La cocaïne, l'imipramine, la desméthylimipramine et la guanéthidine ont provoqué une accumulation accrue de la noradrénaline tritiée dans le vas deferens du rat, dans des conditions expérimentales où elles inhibaient fortement cette accumulation dans le cœur. La réserpine et le métaraminol n'ont pas montré cet effet. La question se pose de savoir si l'accroissement observé est dû à une augmentation de la captation nette de la noradrénaline ou à un échange accru de la noradrénaline exogène et endogène au niveau des terminaisons nerveuses sympathiques du vas deferens.



Effects of cocaine (C), imipramine (I), desmethylimipramine (D), guanethidine (G), L-metaraminol (M), or reserpine (R) on the H^3-norepinephrine accumulation in rat heart and vas deferens. Substances were administered 2 h before an i.v. injection of H^3-norepinephrine. Organs were removed for analysis 1 h after H^3-norepinephrine injection. Values are the means for 3–8 extracts from treated animals ± standard errors of the means. Control values were 1803 ± 61 mμc/g heart (n = 11) and 222 ± 8 mμc/g vas deferens (n = 16).

Effects of cocaine, imipramine, desmethylimipramine (DMI), guanethidine, L-metaraminol and reserpine on the norepinephrine content of heart and vas deferens

Substance	Norepinephrine μg/g wet weight	
	Heart	Vas deferens
NaCl 0.9%	0.76 ± 0.035 (15)	8.22 ± 0.40 (17)
Cocaine	0.79 ± 0.043 (8)	9.33 ± 0.52 (3)
Imipramine	0.78 ± 0.026 (9)	7.40 ± 0.67 (7)
DMI	0.73 ± 0.020 (8)	7.24 ± 0.34 (11)
Guanethidine	0.40 ± 0.045 (7)	9.47 ± 1.03 (3)
L-Metaraminol	0.25 ± 0.014 (3)	10.13 ± 1.44 (3)
Reserpine	0.17 ± 0.012 (8)	5.81 ± 0.65 (4)

Substances were administered as described in the text. Two organs were pooled for each extract. The No. of extracts is given in parentheses.

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