contents of 5-HT (Bloom, Algeri & others, 1969; Breese & Traylor, 1971; Uretsky & Iversen, 1970).

In conclusion, the intraventricular administration of 6-OHDA restored the analgesic action of morphine in morphine-tolerant rats, suggesting that the development of tolerance to morphine analgesia may be at least partly due to changes in the central noradrenaline neurons.

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January 17, 1973

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Dopamine-induced relaxation of isolated arterial strips

The lack of a suitable isolated organ preparation has hampered characterization of the proposed dopamine vascular receptor (van Rossum, 1965; Goldberg, 1972). We undertook the present investigation to search for an isolated arterial strip that would relax upon application of dopamine. We concentrated our efforts on dog renal and mesenteric arteries, since vasodilatation has been observed in these vascular beds in this species (McNay, McDonald & Goldberg, 1963; Eble, 1964; McNay & Goldberg, 1966).

The method used has been previously described (Toda, Usui & others, 1972). Isolated vessels (0·5 to 2 mm outside diameter) were cut into spiral strips of approximately 25 mm in length and were then fixed vertically in a muscle bath of 20 ml capacity containing nutrient solution (in mM concentrations: Na^+, 162·1; K^+, 5·4; Ca^{2+}, 2·2; Cl^-, 157·0; HCO_3^-, 14·9; dextrose, 5·6). The bathing medium was maintained at

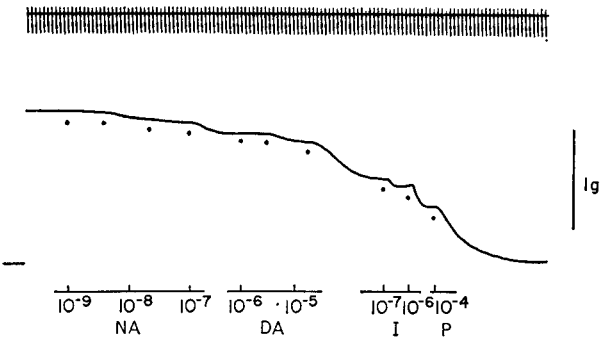

FIG. 1. Relaxation in an isolated mesenteric arterial strip after application of noradrenaline (NA), dopamine (DA), isoprenaline (I) and papaverine (P). The strip was pretreated with phenoxybenzamine, 10^{-5} M for 60 min, and contracted with K^+ (10 mM). Horizontal line signifies the tension before K^+; vertical line signifies 1 g tension. Upper scale, time in min; lower scale, drug dose (M).

$37 \pm 0{\cdot}5°$ and was gassed with 5% carbon dioxide in oxygen. The upper end of the strip was connected to the lever of a force-displacement transducer. The resting tension of the arteries was adjusted to 1·5 g. The preparations were allowed to equilibrate for 90 to 120 min; during this period the medium was replaced at intervals of 20 to 30 min.

When dopamine was applied to the untreated arterial strip, contractions were observed in some preparations and relaxations in others. These different responses could have been due to variations in initial contractile state and α-adrenoceptor sensitivity. Accordingly, subsequent preparations were treated with phenoxybenzamine, 10^{-5} M for 60 min, and after its removal, contracted with K^+ (10 to 30 mM). These modifications resulted in a preparation in which relaxation could be demonstrated consistently. Relaxation was observed at concentrations of dopamine ranging from 10^{-6} to 5×10^{-4} mM in 52 of 56 mesenteric arterial strips obtained from 22 dogs. Similar relaxation was recorded in 13 of 14 renal arterial strips obtained from 8 dogs. Despite the large dose of phenoxybenzamine, initial contraction was also observed in a number of preparations, suggesting the possibility of both α-adrenoceptor and non-adrenergic contraction. Contraction resistant to α-adrenoceptor blockade has also been observed by Furchgott (1972) in studies with phenylephrine and adrenaline.

Fig. 1 shows relaxation in a phenoxybenzamine-treated mesenteric strip following successive applications of noradrenaline, dopamine, isoprenaline and papaverine. The pronounced relaxation produced by dopamine (as with the 2×10^{-5} M dose, Fig. 1) was usually slow to develop and to attain a plateau, in contrast to the rapid response produced by isoprenaline. Such a pronounced relaxing effect of dopamine could not be prevented by prior administration of the β-adrenoceptor blocking agent, sotalol, 10^{-4} M, a dose sufficient to markedly antagonize the relaxing action of isoprenaline. The relaxation produced by dopamine also appeared to be different from that produced by papaverine, since the latter drug almost uniformly caused further relaxation after the maximum response to dopamine.

We have observed apparently similar relaxation following application of dopamine to rabbit, guinea-pig and monkey mesenteric and renal arterial strips and to dog coronary arterial strips. Relaxation, however, could not be demonstrated consistently in dog femoral arterial strips.

These demonstrations of dopamine-induced relaxation in isolated arterial strips support the concept of a specific dopamine vascular receptor. We are currently using these techniques to investigate potential dopamine receptor agonists and antagonists.

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February 15, 1973

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Effects of diethyldithiocarbamate and ethanol on the *in vivo* metabolism and pharmacokinetics of amphetamine in the rat

Recently, Creaven, Barbee & Roach (1970) demonstrated that ethanol and disulfiram diminished the excretion of *p*-hydroxyamphetamine in the urine of rats presumably as a result of blockade of *p*-hydroxylation of amphetamine. We wish to report that pretreatment of rats with the metabolite of disulfiram, diethyldithiocarbamate (DDC), or ethanol causes an increase in the concentrations of subsequently administered amphetamine in brain and plasma.

Male Sprague-Dawley rats, 180–250 g were housed in individual cages at least 24 h before and throughout the experiment. Water and food were freely available. DDC, as the sodium salt, was dissolved in saline and injected in a dose of 400 mg kg^{-1} (s.c.) 1 h before the administration of radioactively labelled amphetamine. Ethanol, 4 g kg^{-1} was given by mouth as a 2·5% solution (v/v) 30 min before the amphetamine injection. (+)-[^{3}H]amphetamine sulphate (generally labelled, New England Nuclear) was adjusted to a specific activity of 1·2 μCi nM^{-1} with unlabelled drug and injected as a saline solution in a dose of 4 mg kg^{-1} (i.p.). (+)-[^{14}C]Amphetamine sulphate (CEA, Gif-sur-Yvette, France) (5 mg kg^{-1}, i.p., 1·3 μCi μM^{-1}) was injected into rats housed individually in metabolic cages. Urine was collected for 24 h. For the determination of brain and plasma concentrations of amphetamine, groups of animals were decapitated at different times (see Fig. 1) after the injection of (+)-[^{3}H]amphetamine. Aliquots of brain extracts (0·4 M perchloric acid, 10 ml/brain) and plasma were adjusted to pH 12 by addition of 1 M sodium hydroxide. (+)-[^{3}H]amphetamine was then extracted into toluene and 1 ml of the organic phase was counted in a scintillation spectrometer provided with an external standard equipment for correction of quenching. Urinary metabolites of [^{14}C]amphetamine were separated by means of paper chromatography and quantified by liquid scintillation counting according to Ellison, Gutzait & van Loon (1966) as described by Lewander (1968).

As shown in Fig. 1a amphetamine disappears from brain and plasma in a polyphasic pattern as previously shown by Maickel, Cox & others (1969) and Lewander (1971). There was a constant concentration ratio between brain and plasma of about 7–8