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THE EFFECTS OF LABETALOL (AH 5158) ON ADRENERGIC TRANSMISSION IN THE CAT SPLEEN

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1 The competitive α- and β-adrenoceptor blocking agent labetalol, in concentrations up to 10^{-4} M, produced dose-dependent increases in transmitter overflow from the isolated blood perfused spleen of the cat following nerve stimulation at 10 and 30 Hz.

2 At concentrations above 10^{-4} M labetalol produced a pronounced decrease in transmitter overflow.

3 Labetalol (1.5×10^{-4} M) increased the recovery of ^{3}H label in the venous blood following the close-arterial infusion of [^{3}H]-(–)-noradrenaline indicating that the drug inhibits uptake of the amine.

4 Both labetalol (3.8×10^{-5} M) and piperoxan (7.4×10^{-6} M) produced parallel shifts to the right of the dose-response curves to noradrenaline and oxymetazoline in isolated strips of cat splenic capsule. In this preparation both drugs acted as competitive postsynaptic α-adrenoceptor blocking agents.

5 Labetalol (3.3×10^{-5} M) increased the transmitter overflow following stimulation of the splenic nerves with 200 impulses at 10 Hz. The overflow could be further increased by subsequent addition of piperoxan (7.2×10^{-6} M). Piperoxan (5.7×10^{-6} M) alone produced a marked increase in transmitter overflow which could be further increased by subsequent addition of desmethylimipramine (DMI; 3.2×10^{-5} M). Cocaine (1.5×10^{-5} M) or DMI (5.4×10^{-5} M) produced a small increase in transmitter overflow which was not further increased by addition of labetalol (2.8×10^{-5} M).

6 Labetalol produced a biphasic effect on the responses of the isolated blood perfused spleen of the cat to nerve stimulation. With low doses (up to 10^{-4} M) vascular responses were potentiated and with high doses (greater than 10^{-4} M) inhibited. The potentiation was related to uptake blockade and the inhibition to decreased transmitter overflow and postsynaptic α-adrenoceptor blockade.

7 Labetalol appears to act as a postsynaptic α-adrenoceptor antagonist in the isolated blood perfused spleen of the cat with little effect on presynaptic α-adrenoceptors. The moderate elevation of transmitter overflow by the drug is related to the inhibitory effect of the drug on neuronal uptake rather than on presynaptic α-adrenoceptors.

Introduction

Release of noradrenaline from sympathetic nerve endings in response to nerve stimulation is controlled by a local feedback mechanism. This feedback is believed to be mediated by α-adrenoceptors located on the presynaptic nerve terminals (Kirpekar & Puig, 1971; Starke, 1972; Enero, Langer, Rothlin & Stefano, 1972; Langar, 1974).

Pre- and post-synaptic α-adrenoceptors appear to differ in their susceptibility to drugs. In the rabbit pulmonary artery the relative potencies of α-adrenoceptor agonists at the two sites were found to vary; methoxamine and phenylephrine were found to act preferentially on postsynaptic α-adrenoceptors; noradrenaline, adrenaline and naphazoline have similar pre- and post-synaptic agonist potencies; and oxymetazoline, α-methyl noradrenaline, tramazoline and clonidine acted preferentially at presynaptic α-adrenoceptors (Starke, Montel, Gayk & Merker, 1974; Starke, Endo & Taube, 1975). In the guinea-pig vas deferens, lysergic acid diethylamide appears to act as a selective presynaptic α-adrenoceptor agonist (Hughes, 1973). Among α-adrenoceptor antagonists similar preferential blockade of one of the two types of α-adrenoceptor can be obtained. Phenoxybenzamine is a more effective blocker of postsynaptic α-adrenoceptors in rat portal vein and cat spleen (Haggendal, Johansson, Jonason & Ljung, 1972; Dubocovich & Langer, 1974). In the rabbit pulmonary artery (Borowski, Ehrl & Starke, 1976) the antagonists ranged in their effects from the post-synaptic α-adrenoceptor blocker clozapine through azapetine, mianserin, phentolamine, dihydroergotamine, piperoxan and tolazoline to a predominantly presynaptic α-adrenoceptor blocker, yohimbine.

Labetalol is an adrenoceptor blocking drug which

produces a competitive blockade of both α- and β-adrenoceptors (Farmer, Kennedy, Levy & Marshall, 1972; Kennedy & Levy, 1975). The following experiments provide evidence to show that labetalol is an antagonist at postsynaptic α-adrenoceptors with little effect on presynaptic α-adrenoceptors in the isolated blood perfused spleen of the cat. A preliminary account of these results has been published (Blakeley & Summers, 1976).

Methods

Overflow of endogenous transmitter

Cat spleens were perfused with blood *in vitro* (Blakeley, Brown, Dearnaley & Woods, 1969; Blakeley, Powis & Summers, 1973). The splenic nerves were stimulated with shielded bipolar platinum electrodes. Supramaximal stimuli of 20 V and 0.5 ms duration were used throughout.

The plan of the experiments in which the effects of labetalol on transmitter overflow were investigated was as follows. Transmitter overflow was stabilized by giving several conditioning trains of stimuli (Bacq, Blakeley & Summers, 1976). Transmitter overflow was then measured following two trains of 200 stimuli at 10 Hz and two similar trains at 30 Hz. On some occasions only 30 Hz was used. Labetalol was then added to the blood in 0.9% w/v NaCl solution (saline) and allowed 20 min to act. Transmitter overflow was then measured following two further periods of stimulation at either 10 or 30 Hz. In any one experiment up to 4 cumulative doses of labetalol were used and the effect on transmitter overflow measured after each dose increment.

Overflowing transmitter in the venous blood was collected for 1 min following stimulation at 30 Hz and for 80 s following stimulation at 10 Hz. The blood collected was chilled, spun and the transmitter in the plasma assayed against (–)-noradrenaline on the blood pressure of the pithed rat (Shipley & Tilden, 1947).

Uptake of [^{3}H]-(–)-noradrenaline

Uptake of [^{3}H]-(–)-noradrenaline was measured from infusions given close arterially, at a rate of 360 ng/min, to the spleen (perfusion rate 6.5 ± 0.6 ml/min, $n=4$). Uptake was taken as the difference between the amount of label given and the amount recovered in the venous blood. This method of measuring uptake entails the acceptance of some errors. Any infusate which is lost through minor bleeding from the spleen, trapped in areas of poor perfusion, or trapped in the red cell layer of the centrifuged samples will tend to elevate uptake when measured by this method. In order to check that this error was not large in any experiment, Evans Blue was added to the infusate to act as an intravascular marker. In the present series of experiments the overall recovery of Evans Blue was $93.7 \pm 4.5\%$ ($n=4$). The results have not been corrected for this recovery.

Isolated strips of cat splenic capsule

Cats (2.4–6 kg) were anaesthetized with 1.5% halothane in N_2O/O_2 (2 : 1 v/v); spleens were removed and washed in Krebs-Bicarbonate solution of the following composition (mM): $NaHCO_3$ 25, NaCl 120, KCl 4.5, NaH_2PO_4 0.19, Na_2HPO_4 1.83, $CaCl_2$ 1.25, $MgSO_4$ 1.00 and glucose 11.1. A 0.5 mm thick layer of the outer capsule of the spleen was sliced off with a modified Stadie–Riggs tissue slicer. The capsular strip was washed with warm Krebs solution and sliced along the long axis of the spleen into pieces measuring approximately 35×4 mm. Pairs of strips were set up in a 25 ml organ bath containing Krebs solution bubbled with 95% O_2 and 5% CO_2 and maintained at 38°C. Contractions of the strips were recorded isotonically under 1 g tension using d.c./d.c. linear variable differential transformer type transducers (Sangamo Weston Controls Ltd. : type ND1 $\pm$ 5 mm stroke) the outputs of which were displayed on a u.v. recorder (SE 3006). Cumulative dose-response curves were obtained for both noradrenaline and oxymetazoline. It was possible to wash out the noradrenaline after obtaining one dose-response curve and repeat the procedure and obtain another dose-response curve which did not differ significantly from the first. Therefore, in the experiments with noradrenaline as the agonist, the α-adrenoceptor antagonist was added between exposures to noradrenaline in the same tissue. However, with oxymetazoline, it was not possible to wash out the drug, so that a comparison between the effects of the α-adrenoceptor antagonists using this agonist was performed on preparations taken from adjacent areas of the same spleen.

Drugs

[7-^{3}H]-(–)-noradrenaline (9.8 mCi/μM); Radiochemical Centre, Amersham) was diluted with (–)-noradrenaline (Sigma) to give a specific activity of 248 μCi/μM; the following drugs were also used: oxymetazoline hydrochloride, Evans Blue (E. Merck, Darmstadt), piperoxan (2-piperidinomethyl-1,4-benzodioxane hydrochloride; Rhone-Poulenc, Paris), cocaine hydrochloride (E. Coburn Ltd.), labetalol (5-(1-hydroxy-2[(1-methyl-3 phenylpropyl)amino] ethyl) salicylamide; Dr G.P. Levy, Allen and Hanbury's Research Ltd.), desmethylimipramine hydrochloride (Pertofran: Geigy Ltd.), heparin (mucus; Boots Ltd.) and prostaglandin E_1 (Dr John E. Pike, Upjohn, Kalamazoo, U.S.A.). All doses of amines are expressed as base.

Unless otherwise defined results are presented as means ± s.e. mean. Significance was assessed by Student's *t* test.

Results

Stabilization of transmitter overflow

The overflow of transmitter following nerve stimulation falls to a plateau after two to three periods of stimulation (Blakeley *et al*, 1969). Series of conditioning stimuli were, therefore, given at the start of each experiment (Bacq *et al.*, 1976). The conditioning periods of stimulation were followed by several control periods of stimulation during which transmitter was collected and assayed. In experiments where the effect of labetalol on overflow following stimulation at 10 Hz was examined, two control periods of stimulation at 30 Hz and two at 10 Hz were given and the transmitter overflows measured. In experiments where the effect of the drug on overflow at 30 Hz was studied only the two periods of stimulation at 30 Hz were given. Table 1 shows that the conditioning periods of stimulation effectively stabilized transmitter overflow following stimulation at both 10 and 30 Hz.

The effect of labetalol on transmitter overflow following nerve stimulation

Labetalol in concentrations up to 10^{-4} M produced a dose-dependent elevation of transmitter overflow at both frequencies of stimulation as shown in Figure 1.

In these experiments transmitter overflow has been expressed as the ratio of the overflow in the presence of the drug compared with the mean overflow obtained after the control periods of stimulation at 30 Hz in the same experiment ($O/\bar{O}_{30}$). This form of expression of transmitter overflow has been used because although the overflow in any one experiment is reproducible, the variation in overflow obtained in different spleens is large (see Table 1 and Blakeley *et al.*, 1969). The elevation of overflow produced by labetalol at 10 Hz was greater than that obtained at 30 Hz so in this respect it resembles other *α*-adrenoceptor antagonists such as dibenamine and phenoxybenzamine (Brown & Gillespie, 1957).

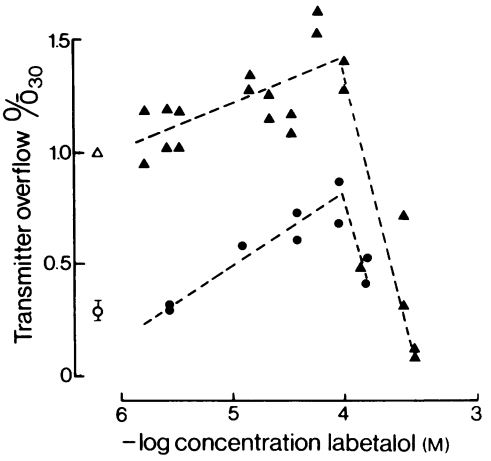

Figure 1 The effect of labetolol on the overflow of transmitter following nerve stimulation in the isolated blood perfused spleen of the cat. Open symbols represent control overflows of transmitter ($O/\bar{O}_{30}$) at 10 Hz (○) and 30 Hz (△) and solid symbols overflows of transmitter in the presence of labetalol following 200 stimuli at 10 Hz (●) and 30 Hz (▲).

At concentrations above 10^{-4} M labetalol produced a pronounced depression of transmitter overflow. We have attributed this effect to the local anaesthetic properties of the drug in high concentrations (Farmer *et al.*, 1972).

The effect of labetalol on uptake of [^{3}H]-(−)-noradrenaline infused into the cat spleen

[^{3}H]-(−)-noradrenaline was infused close arterially into cat spleens at a rate of 360 ng/minute. In the blood perfused cat spleen a steady state condition is reached

Table 1 Effect of conditioning stimulation (3 × 200 stimuli at 10 Hz followed by 2 × 200 stimuli at 30 Hz) on transmitter overflow during control periods of stimulation in the isolated blood perfused spleen of the cat.

	Overflow of transmitter during control periods of stimulation					
	pg/stimulus	n	P	$O/\bar{O}_{30}$	n	P
1st stimulation (200 at 30 Hz)	1195 ± 108	25	>0.7	1.02 ± 0.013	25	<0.05
2nd stimulation (200 at 30 Hz)	1140 ± 95	25		0.98 ± 0.013	25	
3rd stimulation (200 at 10 Hz)	374 ± 51	17	>0.8	0.33 ± 0.036	17	>0.8
4th stimulation (200 at 10 Hz)	364 ± 42	17		0.32 ± 0.031	17	

Overflow expressed as pg/stimulus or as a fraction of the average overflow from the two control periods of stimulation at 30 Hz ($O/\bar{O}_{30}$).

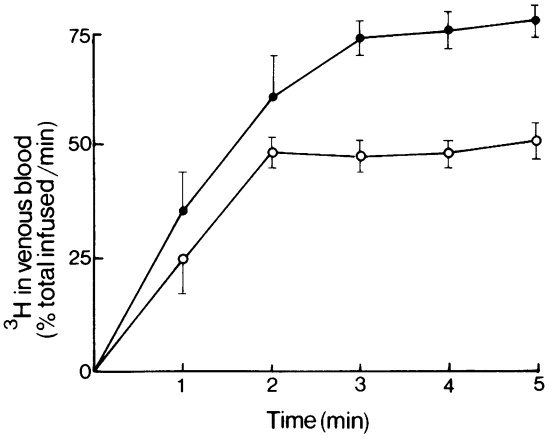

Figure 2 The effect of labetalol on recovery of ^{3}H in the venous blood following close arterial infusion of [^{3}H]-(−)-noradrenaline (360 ng/min) to the isolated blood perfused spleen of the cat. Open symbols (O) represent the recovery of ^{3}H in the absence of drug and the filled symbols (●) the recovery in the presence of labetalol (1.5×10^{-4} M). $n=4$ in each case.

within 2 to 3 min of the start of the infusion (Blakeley, Powis & Summers, 1974). In the absence of drugs the recovery of label infused into the spleen between the 3rd and 5th minutes of infusion was $48.9 \pm 1.9\%$ ($n=12$) as shown by the open symbols in Figure 2. In the presence of labetalol (1.5×10^{-4} M) the recovery of the label in the venous blood is increased to $76.0 \pm 2.0\%$ of that administered ($n=12$; $P<0.001$). The increase in recovery of label in the venous blood indicates that less has been taken up by the spleen and hence it is likely that labetalol is an uptake inhibitor.

The effect of labetalol and piperoxan on the responses of isolated strips of splenic capsule to noradrenaline and oxymetazoline

Labetalol is known to antagonize competitively α-adrenoceptor mediated responses in the guinea-pig mesenteric vein, the rat vas deferens (Farmer *et al.*, 1972) and of the blood pressure in the anaesthetized dog (Kennedy & Levy, 1975). Piperoxan is a classical competitive α-adrenoceptor antagonist (Bacq & Fredericq, 1935; Ariens, 1967) with no inhibitory effects on metabolism or uptake of noradrenaline (Blakeley & Summers, 1975). Both labetalol and piperoxan produced parallel shifts to the right of the dose-response curve to noradrenaline in cat spleen strips as shown in Figure 3a. The doses used were close to those which produced the maximal elevating effect on transmitter overflow.

The shift to the right of the dose-response curve to noradrenaline at the level of the ED_{50} with labetalol (3.8×10^{-5} M) was 5.6-fold whereas with piperoxan

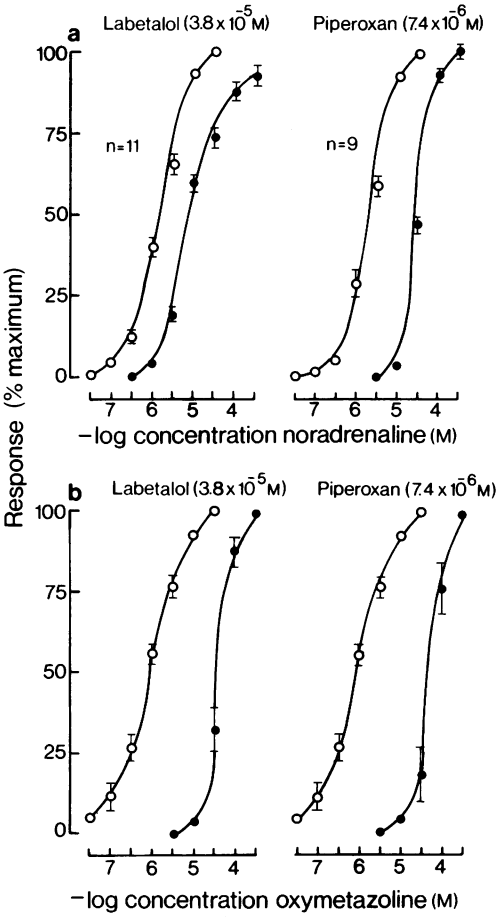

Figure 3 The effect of labetalol and piperoxan on responses of isolated strips of cat splenic capsule (a) to noradrenaline and (b) oxymetazoline. In (a) dose-response curves to noradrenaline were obtained in the same strips before (O) and after (●) exposure to labetalol (3.8×10^{-5} M) or piperoxan (7.4×10^{-6} M) with a 40 min wash between. In (b) the dose-response curves to oxymetazoline were obtained in separate spleen strips in the presence of (●) or in the absence of (O) labetalol or piperoxan, since oxymetazoline does not easily wash out of this preparation.

(7.4×10^{-6}M) it was 13.0-fold. Since, in addition to its α-adrenoceptor blocking properties, labetalol is an inhibitor of noradrenaline uptake and inhibitors of uptake shift the dose-response curve to noradrenaline in spleen strips to the left (Davidson & Innes, 1970; Granata & Langer, 1973; Guimaraes & Brandao, 1973), it is likely that experiments with noradrenaline do not give a true reflection of the α-adrenoceptor blocking properties of the drug. Therefore, in addition to the experiments with noradrenaline as an agonist, experiments were performed using another α-

adrenoceptor agonist, oxymetazoline (Mujic & Van Rossum, 1965) which is not a substrate for uptake$_1$ (Birmingham, Paterson & Wojcicki, 1970). In these experiments, shown in Figure 3b, both labetalol (3.8×10^{-5} M) and piperoxan (7.4×10^{-6} M) produced similar parallel shifts to the right of the dose-response curve, and labetalol was 5.1 times less potent than piperoxan. The experiments provide evidence to show that both labetalol and piperoxan are competitive postsynaptic α-adrenoceptor antagonists in isolated strips of cat splenic capsule.

Investigation of the mechanism of the effect of labetalol on transmitter overflow

The elevation of overflow produced by labetalol is likely to involve inhibition of (–)-noradrenaline uptake or blockade of presynaptic α-adrenoceptors or both. The effects of labetalol on transmitter overflow were therefore compared with those of the known uptake$_1$ blockers DMI and cocaine, and with a presynaptic α-adrenoceptor antagonist without uptake blocking properties, piperoxan (Blakeley & Summers, 1975). The additive effects of labetalol with these was also investigated. The results of these experiments are presented in Table 2. Labetalol and piperoxan individually elevated transmitter overflow and their effects were additive. After uptake$_1$ blockade, labetalol produced no further increase in overflow (changes greater than 25% should have been detected in these experiments whereas a presynaptic α-adrenoceptor blocker might have been expected to produce an increase greater than 300%). The doses of piperoxan used were both supramaximal for their elevating effect on transmitter overflow (Blakeley & Summers, 1975). The slope of the dose-response curve for labetalol (see Figure 1) is not steep and a similar effect would have been expected with both doses used.

Effect of labetalol on responses of the spleen to nerve stimulation

Following stimulation of the splenic nerves with 200 supramaximal stimuli at 10 Hz the spleen responds with increases in perfusion pressure (vascular responses) and with contractions of the splenic capsular smooth muscle (seen as increases in venous blood flow) as shown in Figure 4a.

As with the effect on transmitter overflow, labetalol produced a biphasic effect on vascular and capsular responses of the spleen to nerve stimulation. At low doses, responses were potentiated and at high doses, inhibited. The potentiation observed with labetalol (Figure 4b) is not as pronounced as that observed with cocaine in this preparation (Cripps & Dearnley, 1972) and probably represents the resultant of the inhibition of uptake and postsynaptic α-adrenoceptor blockade. The inhibition of responses (Figure 4c) with higher doses is probably due to the inhibitory effect of the drug on release of transmitter and the postsynaptic α-adrenoceptor blocking effect.

Discussion

The isolated blood perfused spleen of the cat has been

Table 2 The effect of drugs on the overflow of transmitter in the isolated blood perfused spleen of the cat following nerve stimulation with 200 stimuli at 10 Hz.

	Drug concentration (M)	*Transmitter overflow* ($O/\bar{O}_{30}$)	n	P
Control	–	0.32 ± 0.02	21	
				<0.001
Labetalol	3.3×10^{-5}	0.75 ± 0.09	8	
				<0.001
Labetalol + Piperoxan	3.3×10^{-5} + 7.2×10^{-6}	1.44 ± 0.12	8	
				<0.05
Piperoxan	5.7×10^{-6} M	1.11 ± 0.08	14	
				<0.05
Piperoxan + DMI	5.7×10^{-6} M + 3.2×10^{-5} M	1.45 ± 0.17	4	
DMI or cocaine	5.4×10^{-5} or 1.5×10^{-5}	0.48 ± 0.04	8	
				>0.3
DMI or cocaine + labetalol	5.4×10^{-5} or 1.5×10^{-5} + 2.8×10^{-5}	0.42 ± 0.04	8	

Overflow is expressed as a fraction of the mean overflow obtained after two control periods of stimulation at 30 Hz ($O/\bar{O}_{30}$).

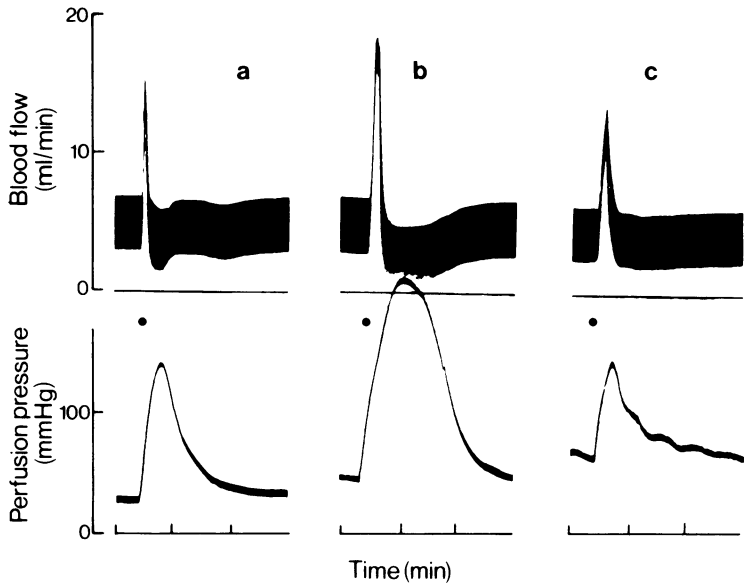

Figure 4 The effects of labetalol on the change in vascular resistance and venous blood flow in the isolated blood perfused spleen of the cat following nerve stimulation with 200 stimuli at 10 Hz. (●). (a) Control; (b) 20 min after labetalol (2.1×10^{-5} M); (c) 20 min after labetalol (3.4×10^{-4} M). Time marks, 1 minute.

used to examine the pharmacology of labetalol, a drug which has the unusual property of being a competitive blocker of both α- and β-adrenoceptors (Farmer *et al.*, 1972). Many α-adrenoceptor antagonists such as dibenamine (Brown & Gillespie, 1957), hydergine (Blakeley, Brown & Ferry, 1963; Cripps & Dearnaley, 1972), phentolamine (Kirpekar & Puig, 1971; Cubeddu, Barnes, Langer & Weiner, 1974) and piperoxan (Blakeley & Summers, 1976), are known to increase transmitter overflow following stimulation of the splenic nerves. There is now abundant evidence that these drugs elevate overflow by blockade of an inhibitory feedback loop acting via α-adrenoceptors located on the presynaptic nerve terminals (Kirpekar & Puig, 1971; Starke, 1972; Enero *et al.*, 1972; Langer, 1974).

The present experiments show that labetalol increases transmitter overflow on nerve stimulation. The mechanism of this elevation does not involve inhibition of presynaptic α-receptors. The evidence for this conclusion was that the preferential presynaptic α-adrenoceptor blocker, piperoxan (Borowski, *et al.*, 1976) given after labetalol produces a further increase in overflow and the fact that labetalol given after uptake$_1$ blockade fails to produce any marked increase in overflow. The overflow obtained in the presence of both labetalol and cocaine was less than that obtained with labetalol alone. The reason for this may lie in the patterns of overflow obtained after treatment of the spleen with these drugs. Labetalol alone produced no change in the pattern of overflow of transmitter. Cocaine on the other hand considerably prolongs the overflow of transmitter (Cripps & Dearnaley, 1972; Cubeddu *et al.*, 1974) so that collection of venous blood for 80s would result in collection of only a fraction of the total transmitter overflowing.

Those results obtained with cocaine and DMI also suggest that the mechanism whereby labetalol increases overflow is blockade of uptake$_1$. There is now evidence which supports this conclusion. In the present experiments in the spleen, labetalol increased the recovery of ^{3}H in the venous blood following infusion of [^{3}H]-(–)-noradrenaline: the drug has been shown to block a cocaine-sensitive uptake process in the anaesthetized dog (Farmer *et al.*, 1972) and it inhibits production of the neuronally produced metabolite 3 : 4 dihydroxyphenyl-ethylene glycol in the cat spleen (Summers & Tillman, 1976). The experiments in spleen strips also support this conclusion. Labetalol was a less potent antagonist of noradrenaline than piperoxan, both drugs being given in concentrations that were optimum for elevating overflow. However, when the agonist used was oxymetazoline, an α-adrenoceptor agonist (Mujic & Van Rossum, 1965) which is not a substrate for uptake$_1$ (Birmingham *et al.*, 1970), both drugs were similar in their effectiveness as α-receptor blockers. It is likely that when noradrenaline is the agonist the uptake blocking properties of labetalol prevent its true α-adrenoceptor blocking properties from being seen.

The experiments in spleen strips confirm that labetalol is a postsynaptic α-adrenoceptor blocker in

the cat spleen as in guinea-pig mesenteric vein, rat vas deferens (Farmer *et al.*, 1972) and on dog blood pressure (Kennedy & Levy, 1976). This would indicate that in the cat spleen labetalol is a preferential antagonist of postsynaptic α-receptors.

However, there are other explanations which must be considered. The first concerns the presence of a β-adrenoceptor mediated positive feedback mechanism at adrenergic nerve endings (Adler-Graschinsky & Langer, 1975). In guinea-pig atria, isoprenaline increases and propranalol decreases output of label following nerve stimulation. Although it is not known whether there are presynaptic β-adrenoceptors in the spleen the fact that labetalol is a competitive β-adrenoceptor antagonist (Farmer *et al.*, 1972) raises the possibility that it could act through this mechanism. Its relative lack of effect on transmitter overflow could be due to the antagonistic effects on α-adrenoceptors tending to produce an increase, and β-adrenoceptor blockade tending to produce a decrease. We do not favour this explanation for several reasons. Firstly, the effects of β-adrenoceptor blockers are too small to explain the effects observed in the present experiments in the spleen. Secondly, in the spleen the addition of sotalol, a β-adrenoceptor antagonist without β stimulant activity or membrane stabilizing effects (Barrett & Carter, 1970) produced a small decrease in transmitter overflow but did not affect the elevation produced by labetalol (Blakeley & Summers, unpublished observations). One would expect in these circumstances that following β-adrenoceptor blockade the presynaptic α-adrenoceptor blocking effects of labetalol would be revealed, leading to a large increase in overflow. This did not occur. Another factor to be considered is the local anaesthetic property that labetalol is reported to have (Farmer *et al.*, 1972). A local anaesthetic effect could explain the abrupt decrease in overflow seen with high doses but does not appear to be important at lower dose levels since piperoxan was still able to elevate overflow considerably in the presence of these concentrations.

In conclusion we have provided evidence that labetalol is a preferential postsynaptic α-adrenoceptor antagonist in the cat spleen. The moderate elevation of overflow which the drug produces in doses up to 10^{-4}M is primarily due to inhibition of transmitter uptake rather than inhibition of presynaptic α-adrenoceptors.

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