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THE EFFECTS OF (+)- AND (−)-PROPRANOLOL ON ^{3}H-TRANSMITTER EFFLUX IN GUINEA-PIG ATRIA AND THE PRESYNAPTIC β-ADRENOCEPTOR HYPOTHESIS

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1 The effects of isoprenaline and of the (+)- and (−)-isomers of propranolol on the stimulation-induced overflow of ^{3}H-transmitter was assessed in guinea-pig atria to evaluate the hypothesis of presynaptic β-adrenoceptors.

2 Isoprenaline (1.2×10^{-8} M) enhanced the efflux of tritium at 2 and 5 Hz with 100 pulses and did so to a similar extent at both frequencies.

3 The (−)-isomer of propranolol (1.0×10^{-7} M) blocked the enhancing effect of isoprenaline but did not by itself modify transmitter efflux.

4 The (+)-isomer of propranolol, almost devoid of β-adrenoceptor blocking properties, was also effective at 1.0×10^{-7} M in blocking the enhancement of tritium efflux by isoprenaline.

5 The (−)-isomer of propranolol (1.0×10^{-7} M) blocked almost entirely the inotropic response to isoprenaline (3×10^{-7} M) but even 3.0×10^{-6} M (+)-propranolol was inneffective in antagonizing the β-adrenoceptor-mediated contractile responses to the catecholamine.

6 It is concluded that the presynaptic site of isoprenaline action does not show the requisite stereospecifity of β-adrenoceptors and that a 'non-specific' action of the antagonist probably accounts for its reduction of the effect of isoprenaline.

Introduction

The identification and rapid acceptance of an α-adrenoceptor system located presynaptically and mediating inhibition of stimulation-induced transmitter output has led to a search for presynaptic β-receptors to support further a parallel between presynaptic and postsynaptic adrenergic mechanisms (Langer, 1977; Starke, 1977; Westfall, 1977). The enhancement of stimulation-induced [^{3}H]-noradrenaline efflux by isoprenaline in guinea-pig atria, cat aorta, spleen and nictitating membrane has been interpreted as indicating the presence of functional presynaptic β-receptors which may serve a positive feedback role modulating transmitter output (Langer, Enero, Adler-Graschinsky, Dubocovich & Celuch, 1975; Adler-Graschinsky & Langer, 1975). This excitatory system is presumed to be activated by endogenously released noradrenaline under conditions of low frequency stimulation (Langer *et al.*, 1975; Langer, 1976; 1977).

The present experiments were done to discover whether the effects of isoprenaline on stimulation-induced ^{3}H-transmitter efflux are attributable to a specific interaction with presynaptic β-receptors or if they might instead be due to some other, perhaps less specific, action of the catecholamine.

Methods

Tissue preparation

Left atria were removed from albino guinea-pigs of either sex (300 to 600 g) after death by cervical dislocation, cut into halves lengthwise from base to apex as previously described (Furchgott & Garcia, 1968; Furchgott, Garcia, Wakade & Cervoni, 1971) and immersed in cold (4°C) and oxygenated (95% O_2: 5% CO_2) Krebs–Henseleit (Krebs) solution (NaCl 115.3, KCl 4.6, $CaCl_2$ 2.3, $MgSO_4$ 1.1, $NaHCO_3$ 22.1, KH_2PO_4 1.1, glucose 7.8 and disodium edetate, 0.03 mM). The atria were then incubated for 60 min in 4.0 ml of oxygenated Krebs solution containing (−)-[7,8-^{3}H]-noradrenaline (10 μCi/ml, 7.6 to 10.0×10^{-7} M) at 37°C. Following a wash with fresh Krebs solution at the end of the incubation period, the preparations were mounted in a superfusion apparatus and equilibrated under 2 g tension for 90 min. Preparations were superfused continuously with warmed (37°C) and oxygenated Krebs solution by a gravity feed system which maintained a flow rate of 5 ml/min and mechanical responses were recorded isometrically with force-displacement transducers and a Grass Polygraph.

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Stimulation parameters and protocols

The atrial halves were suspended between platinum wire electrodes such that one electrode was attached to the apex and the other surrounded the base of the tissue. The preparations were stimulated transmurally. Each tissue received at 9 min intervals, 100 biphasic pulses of 1.0 ms duration and supramaximal voltage, twice at each of the test frequencies, namely 2 Hz and 5 Hz, using Grass model S5 stimulators.

In experiments with propranolol either the (+)- or (−)-isomer (incorporated into Krebs solution) was superfused onto one of the two halves of each left atrium 20 min before the start of the first series of stimulations, and maintained throughout the duration of the experiment. Upon completion of the initial series of stimulations, isoprenaline (also incorporated into the Krebs solution) was superfused onto both control and treated preparations. Twenty minutes after the introduction of isoprenaline, with agonist and antagonist present, a second identical series of stimulations was performed. The period between the initial exposure to (−)- or (+)-propranolol and the introduction of isoprenaline was approximately 60 min. Cocaine (8.8×10^{-6} M) and normetanephrine (1×10^{-5} M) were routinely present in the Krebs solution throughout all experiments, to eliminate any complications due to the involvement of drug action on either neuronal or extraneuronal uptake of noradrenaline.

Drugs and radiochemicals

The drugs used and their sources were: cocaine hydrochloride (Allen & Hanburys), (±)-normetanephrine hydrochloride (Calbiochem), (+)-propranolol (Ayerst), (−)-propranolol hydrochloride (Ayerst), and (±)-isoprenaline hydrochloride (Winthrop Laboratories). The radioisotope, 1-[7,8-^{3}H]-noradrenaline hydrochloride (specific activity 10 to 13 Ci/mmol) was obtained from the Radiochemical Centre, Amersham. It was diluted to a stock concentration of 100 μCi/ml in (−)-ascorbic acid solution (50 μg/ml) and stored at 4°C in 5 ml aliquots under nitrogen gas. To obtain a final concentration of 10 μCi/ml (7.6 to 10.0×10^{-7} M) in the incubation medium, 0.4 ml of this stock solution was added to 3.6 ml of Krebs solution. The cocaine (3 μg/ml; 8.8×10^{-6} M), normetanephrine (2.2 μg/ml; 1×10^{-5} M), (−)-propranolol (30 μg/ml; 1×10^{-7} M), (+)-propranolol (30 μg/ml; 1×10^{-7} M) and isoprenaline (30 μg/ml; 1.2×10^{-8} M) were dissolved directly into the Krebs solution.

Efflux of [^{3}H]-noradrenaline

The efflux of [^{3}H]-noradrenaline from the preparations was determined by counting 1.0 ml aliquots of the 15.0 ml superfusate collected in vials by a fraction collector which rotated once every 3 min. The aliquots were then transferred to vials containing 10 ml of Aqueous Counting Scintillant (Amersham) and counted to a 1% error in a Beckman LS-230 counter with automatic external standardization to determine efficiency.

Basal efflux is expressed as disintegrations per minute (d/min) and referred to as the total radioactivity detected in the 3 min sample collected immediately prior to each stimulation. Stimulation-induced efflux was calculated as the difference between basal efflux and the total d/min detected in the 3 min sample collected during and after stimulation. Transmural stimulation was always begun at the start of a 3 min collection period.

Mean data on efflux are presented with their standard errors and Student's paired t test was used for all comparisons between treated and untreated atrial halves with the unpaired test used for all other comparisons. P values of less than 0.05 were considered significant.

Results

Effects of isoprenaline on [^{3}H]-noradrenaline efflux

Guinea-pig left atria responded to field stimulation at 2 Hz and 5 Hz with distinct increments in the efflux of [^{3}H]-noradrenaline. The total efflux of tritium with 100 pulses (S_1) in untreated atria, corrected for basal efflux, did not differ significantly between the two frequencies (Table 1). Isoprenaline at 1.2×10^{-8} M, the concentration previously reported to activate presynaptic β-receptors (Adler-Graschinsky & Langer, 1975; Langer *et al.*, 1975), was administered to one of each pair of half-atria after the initial stimulation cycle was completed. Twenty minutes later, stimulations were repeated in both the untreated and agonist-treated preparations. The effect of the drug was assessed by comparison of the efflux ratios between first and second stimulation runs in control and treated atrial halves taken from the same heart. The β-receptor agonist elevated significantly the efflux of tritium at both test frequencies (Table 1). The stimulation-induced efflux of tritium in the presence of isoprenaline, as manifested by the S_2/S_1 ratio, in six half-atria at 2 and 5 Hz was 125.9 ± 7.0% and 136.6 ± 10.8%, respectively of the corresponding values for six matching untreated half-atria, and these increments did not differ significantly from each other. The relative effectiveness of isoprenaline at the two test frequencies was further compared by extending the observations to an additional 12 preparations treated with the catecholamine and pooling these with all the isoprenaline treated groups shown in Table 1. As can

be seen in Table 1, in a total of 32 preparations, the effect of the agonist on transmitter efflux (S_2/S_1 ratios) did not differ significantly between the two test frequencies.

Effects of propranolol isomers

To assess the effectiveness of (−)-propranolol as an antagonist of the isoprenaline-induced enhancement of tritium efflux, one of each pair of half-atria was pretreated, before stimulation, with the β-receptor blocking agent at 1×10^{-7} M, a concentration shown previously to block the presynaptic effect of isoprenaline in cat spleen (Celuch, Dubocovich & Langer, 1978), followed after 20 min, without washout, by stimulation with 100 pulses at 2 and at 5 Hz. After recovery from these initial tests and in the continued presence of (−)-propranolol, both the six control and six treated atrial halves, taken from the same hearts, were exposed to isoprenaline (1.2×10^{-8} M) and then 20 min later re-stimulated with the indicated test frequencies. This low concentration of the β-receptor antagonist blocked completely the isoprenaline-induced enhancement of efflux at both test frequencies as determined from the overflow ratios (Table 1).

The (+)-isomer of propranolol has negligible β-receptor blocking properties at moderate concentrations (Barrett & Cullum, 1968; Eliash & Weinstock, 1971; Mylecharane & Raper, 1973) and it was used to determine the specificity of action of (−)-propranolol. A protocol similar to that described for the (−)-isomer revealed that the identical concentration of the (+)-isomer (1×10^{-7} M) also was effective in antagonizing the effects of the catecholamine on tritium efflux (Table 1). Additionally, comparisons of the ratios (S_2/S_1) of tritium efflux in atria exposed to isoprenaline in the presence and absence of either the (+)- or the (−)-isomer revealed no significant differences in the effectiveness of the two isomers as antagonists at either 2 or 5 Hz (Table 1). Further, both isomers restored the efflux ratios to values obtained in preparations not exposed to the β-receptor agonist between stimulation runs. Neither isomer of propranolol, used alone, modified significantly the efflux of

Table 1 The effects of isoprenaline and of (+)- and (−)-propranolol on stimulation-induced efflux of [^{3}H]-noradrenaline in atria

Stimulation frequency	*No. of values*	*Pretreatment**	*Transmitter overflow (d/min × 10^3) 1st stimulation period (S_1)*	*Treatment†*	*Transmitter overflow ratio S_2/S_1*	*P value*
2 Hz	6	—	21.8 ± 2.1	—	(a) 0.98 ± 0.04	(a) vs (b) <0.02
	6	—	18.4 ± 2.3	Isoprenaline	(b) 1.22 ± 0.05	(a) vs (c) <0.001
	32	—	21.0 ± 1.4	Isoprenaline	(c) 1.23 ± 0.03	
	6	—	26.7 ± 3.2	Isoprenaline	(d) 1.25 ± 0.07	(d) vs (e) <0.01
	6	(−)-Propranolol	30.0 ± 4.7	Isoprenaline	(e) 0.93 ± 0.04	(e) vs (a) NS
						(e) vs (c) <0.001
	8	—	23.7 ± 3.5	Isoprenaline	(f) 1.26 ± 0.04	(f) vs (g) <0.01
	8	(+)-Propranolol	22.0 ± 1.5	Isoprenaline	(g) 1.04 ± 0.05	(g) vs (a) NS
						(g) vs (c) <0.01
						(g) vs (e) NS
5 Hz	6	—	24.5 ± 2.1	—	(h) 0.97 ± 0.04	(h) vs (i) <0.01
	6	—	20.0 ± 1.9	Isoprenaline	(i) 1.32 ± 0.09	(h) vs (j) <0.001
	32	—	23.9 ± 1.6	Isoprenaline	(j) 1.25 ± 0.03	
	6	—	31.2 ± 3.5	Isoprenaline	(k) 1.20 ± 0.04	(k) vs (l) <0.001
	6	(−)-Propranolol	35.4 ± 5.4	Isoprenaline	(l) 0.90 ± 0.04	(l) vs (h) NS
						(l) vs (j) <0.001
	8	—	26.7 ± 4.0	Isoprenaline	(m) 1.20 ± 0.05	(m) vs (n) <0.01
	8	(+)-Propranolol	25.9 ± 1.9	Isoprenaline	(n) 0.98 ± 0.03	(n) vs (h) NS
						(n) vs (j) <0.001
						(n) vs (l) NS

Isoprenaline (1.2 ± 10^{-8} M) or (+)- or (−)-propranolol (1×10^{-7} M) were administered as described in text. The number of values refers to the number of preparations tested. Each frequency with 100 pulses was repeated twice during the first run (S_1) and twice during the second run (S_2) with each atrium and mean values obtained. Values are shown with their standard errors. *P* values <0.05 were considered significant.

* Drug given prior to S_1 and maintained throughout experiment.

† Drug given between S_1 and S_2 and maintained through S_2.

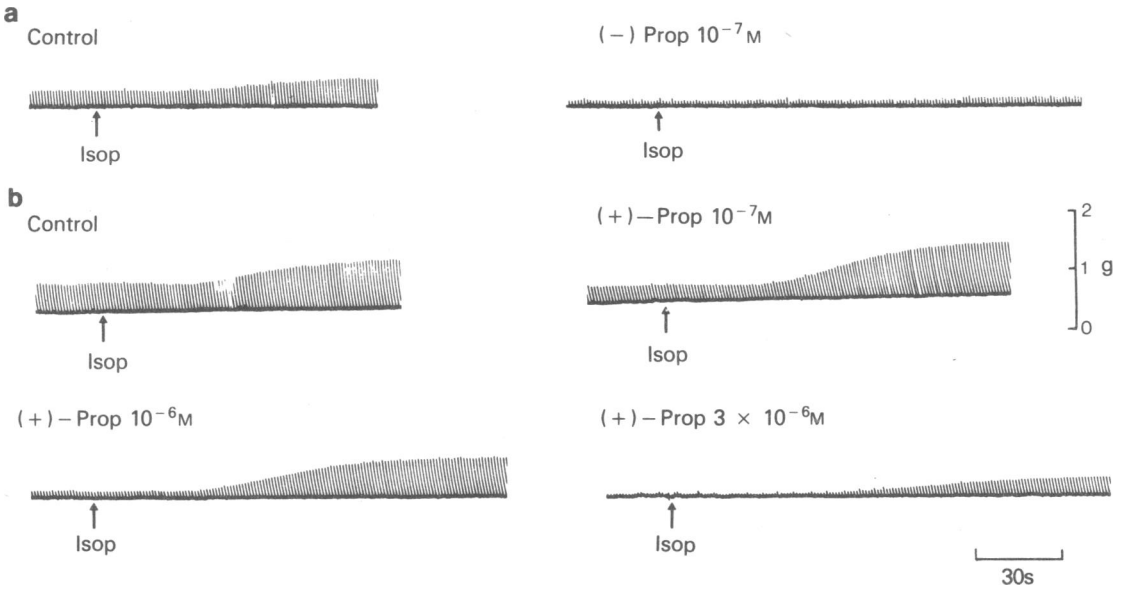

Figure 1 Effect of propranolol (Prop) on responses to isoprenaline (Isop) in field stimulated left atrial preparations of guinea-pig. (a) Effect of isoprenaline (1.2×10^{-8} M) on the inotropic response to field stimulation at 1 absence and presence of (−)-propranolol. (b) Effect of isoprenaline (1.2×10^{-8} M) on the inotropic response to field stimulation at 1 Hz in the absence and presence of (+)-propranolol at the three indicated concentrations.

tritium as determined by comparisons of ^{3}H-transmitter efflux during the first period of stimulation (S_1) in untreated and treated preparations (Table 1).

Effects of propranolol on contractions

In four left atria the effect of isoprenaline on the magnitude of contractions to field stimulation at 1 Hz was assessed in the presence and absence of (+)- or (−)-propranolol, as shown in Figure 1. Exposure of atria to (+)- or (−)-propranolol (1×10^{-7} M) for 60 min depressed the inotropic response to field stimulation by 42.1 ± 4.1% and 57.9 ± 7.9%, respectively. In addition, incubation with (−)-propranolol (1×10^{-7} M) severely curtailed the peak magnitude of the inotropic response to isoprenaline (3×10^{-7} M), measured as a percentage of the contraction height to field stimulation prior to the addition of the catecholamine. The β-antagonist reduced it from 159.6% to 115.9% of the pre-isoprenaline amplitude. The (+)-isomer had no such blocking effect on responses to the catecholamine. Whereas the peak effect of isoprenaline in the absence of the (+)-isomer was to increase contractile tension to 155% of the pre-isoprenaline level, in the presence of 1×10^{-7} M, 1×10^{-6} and 3×10^{-6} M (+)-propranolol, the peak amplitudes of response were 304.3, 385.6 and 295.8% of the responses to field stimulation immediately before the addition of the catecholamine.

Discussion

The elaboration of presynaptic receptor theory to include the participation of β-adrenoceptors opposite in function to the predominant α-receptors has not been accepted uncritically (e.g. Farnebo & Hamberger, 1974; Starke, 1977). Although a parallel to postsynaptic events may be drawn to substantiate the probable existence of such receptors, the available evidence is quite limited both in scope and in variety. Whereas β-receptors located postsynaptically, in tissues which respond neurogenically with α-receptor mediated responses, have not been assigned any special autonomic function, this has not been the case presynaptically. It has been proposed that the duality in presynaptic receptor composition allows transmitter output to reflect more appropriately than otherwise would be possible, the dynamics of the responding system (Langer, 1977).

Under conditions of low frequency stimulation it is presumed that β-receptor activation assists transmission by enhancing quantal release and thus the dependent response but that under more vigorous stimulation the predominant α-inhibitory receptors are involved in mitigation of transmitter release and the concomitant response. The critical evidence which is purported to verify the existence of neuronal β-receptors is that isoprenaline enhances the stimulation-induced output of ^{3}H-transmitter in

several test preparations (e.g. Adler-Grashinsky & Langer, 1975; Stjärne, 1975; Langer *et al.*, 1975) and the associated recent report that propranolol blocks this effect in cat spleen (Celuch *et al.*, 1978). However, some workers (Farnebo & Hamberger, 1974; Starke, Endo, Taube & Borowski, 1975; Endo, Starke, Bangerter & Taube, 1977) have failed to observe an effect of isoprenaline on the stimulation-induced tritium efflux in rabbit pulmonary artery, mouse atria and rat cerebral cortex, raising doubts as to the general applicability of the earlier positive findings.

The present work was done to obtain more information as to the kind of effects exerted by isoprenaline and propranolol on transmitter efflux. The β-receptor antagonist is known to have other actions on neuronal tissue, such as local anaesthetic (Hermansen, 1969), as well as a well-documented myocardial depressant effect (van Zwieten, 1969), and the relationship of these less specific manifestations to the assumed presynaptic receptor activity of propranolol has not yet been examined.

In the present study, the finding of Adler-Grashinsky & Langer (1975) that isoprenaline at 1×10^{-8} M increased the stimulation-induced efflux in guinea-pig atria was confirmed. However, propranolol by itself did not decrease efflux, in contrast to the observation of these previous workers. Others have also described the inability of propranolol to reduce stimulation-induced efflux in various test preparations (Langer *et al.*, 1975; Starke *et al.*, 1975; Stjärne & Brundin, 1976) and some have interpreted this as signifying a minor physiological role for presynaptic β-receptors under ordinary conditions of neuronal excitation.

The central aspect of the present study was the finding that the effect of isoprenaline on tritium efflux was blocked successfully not only by (−)-propranolol, in the standard concentration employed by others to demonstrate the specificity of the presynaptic effect (1×10^{-7} M) (e.g. Celuch *et al.*, 1978), but also by a similar concentration of (+)-propranolol, the isomer with greatly diminished blocking properties. It has been shown elsewhere that the dextro-isomer, although less than one hundredth as potent as the laevo-isomer as a cardiac β-adrenoceptor antagonist, is roughly equipotent to it as a myocardial depressant and as a local anaesthetic and neuronal blocking agent in several test preparations (Vaughan Williams, 1966; Barrett & Cullum, 1968; Hermansen, 1969; Barrett & Nunn, 1970; Eliash & Weinstock, 1971; Mylecharane & Raper, 1973). It appears likely from the present data that the blunting of the isoprenaline effect is more intimately tied to a 'non-specific' action of a moderate concentration of the propranolol isomers than to the occupation of discrete β-receptor sites, which are acknowledged to show marked stereospecificity. The ineffectuality of the (+)-isomer as a β-receptor antagonist at postsynaptic receptor sites is clearly shown in the present experiments; whereas a concentration of 1×10^{-7} M of the (−)-isomer blocked almost totally the inotropic effect of isoprenaline (3×10^{-7} M), even 3×10^{-6} M of the (+)-isomer proved ineffective. However, both isomers exerted an obvious myocardial depressant effect at 1×10^{-7} M, as determined by the magnitude of isometric contractions to field stimulation.

It has been maintained that 'During noradrenaline release at low frequencies of nerve stimulation the positive feedback mechanism mediated by presynaptic-β-adrenoceptors is activated leading to an increase in transmitter release. As the concentration of released noradrenaline increases, a threshold is reached at which the negative feedback mechanism mediated by presynaptic α-adrenoceptors is triggered leading to inhibition of transmitter release' (Langer, 1977). However, the argument made to establish a physiologically meaningful reciprocity in the operation of presynaptic α- and β-receptors does not withstand scrutiny. In support of the contention that low frequency stimulation preferentially activates presynaptic β-receptors and that more intense frequencies are necessary to activate α-receptors, Langer (1977) comments that in most tissues 'concentrations of noradrenaline required for stimulation of postsynaptic α-receptors are about 100× higher than those necessary to stimulate the postsynaptic β-receptors'. By extrapolation of these relative potency differences to presynaptic loci, a substantiation of the hypothesis of a compatible α- and β-system regulating release is offered. However, no such potency relationship occurs postsynaptically. In fact, the affinity between noradrenaline and postsynaptic receptors is greater for the α than for the β, when a number of systems are surveyed (Table 2). The mean pD_2 values in 13 tissues each for α- and β-mediated responses was 6.45 and 5.36, respectively. Although β_1-receptors have a greater affinity for noradrenaline than do β_2-receptors, the presynaptic sites which interact with isoprenaline do not clearly fall into the former category (Dahlöff, Áblad, Borg, Ek & Waldeck, 1975; Stjärne & Brundin, 1976). β_2-Receptor agonists but not a β_1-agonist enhanced transmitter efflux in human omental artery and vein preparations (Stjärne & Brundin, 1976). In addition, as was emphasized by Starke (1977), inhibition of transmitter overflow (α) by endogenously released noradrenaline must occur at exceedingly low frequencies based on the effect of phentolamine to increase overflow, even below 1 Hz.

Other evidence used to support the interpretation of β-receptor function proposed by Langer (1977) is that isoprenaline exerts its maximal enhancing effect on efflux at 1 to 2 Hz and has a much lesser effect at 4 to 5 Hz (e.g. cat aorta, cat spleen, Langer *et al.*, 1975). But is is necessary to appreciate that the relative effec-

tivensss of the externally added agonist in enhancing stimulation-induced efflux at any given frequency is not directly but inversely related to the degree of existing β-presynaptic receptor activation by released transmitter at that particular frequency. Thus, a large efflux-enhancing effect by isoprenaline at 1 but not at 4 Hz must indicate *not* that the presynaptic sites are largely activated by locally released noradrenaline at the lower frequency, but the opposite condition. The sites, unoccupied by locally released transmitter are available to be activated by isoprenaline at 1 or 2 Hz but at 4 or 5 Hz if they are activated by transmitter noradrenaline little more can be achieved by the addition of exogenous agonist. The amount of the difference in stimulation-induced efflux in the presence and absence of isoprenaline will diminish with increasing frequency, over a reasonable range, if the presynaptic β-sites are increasingly activated by locally released noradrenaline. This will be the case, regardless of the level of α-site activation. Once the frequency is reached at which the β-receptors are saturated by endogenously liberated noradrenaline, the added isoprenaline should have a negligible additional effect. Thus, the information provided by proponents (e.g. Langer, 1977), interpreted in terms of presynaptic receptor theory, would signify that the β-sites are contributing more fully as a determinant of neuronal secretion at the higher than at the lower frequencies. In the present experiments the effect of isoprenaline did not differ between 2 and 5 Hz, a finding also incompatible with the postulated operation of a positive feedback system sensing the perineuronal level of transmitter.

A demonstrable discrepancy in the proposed role of isoprenaline-sensitive sites and the so-called α-adrenoceptor sites then becomes apparent: the α- and β-receptor systems are both simultaneously activated over a similar frequency range by transmitter noradrenaline as determined by the maximal and minimal effects of exogenous agonist. For example, the maximal inhibitory effect of noradrenaline and the maximal enhancing effect of isoprenaline both occur at 1 Hz (e.g. guinea-pig atria, Kalsner, unpublished; cat spleen, Langer *et al.*, 1975; Langer, 1977). Similarly both agonists show minimal effects at identical frequencies (Langer, 1977). Instead of explaining the existing data in terms of a positive feedback system it appears more likely that the effect of isoprenaline

Table 2 Adrenoceptor potency of noradrenaline

Species	*Tissue*	*Adrenoceptor*	*pD_2†*	*Source*
Cat	Nictitating membrane	α	6.00*	Langer & Trendelenburg, 1969
	Spleen	α	8.16*	Reiffenstein, 1968
Dog	Cerebral artery	α	7.15*	Allen, Henderson, Chou & French, 1974
	Saphenous vein	α	7.11*	Guimarães & Osswald, 1969
Guinea-pig	Aorta	α	7.17*	Guimarães, 1972
Mouse	Spleen	α	7.04	Ignarro & Titus, 1968
Rabbit	Aorta	α	7.36*	Kalsner, Nickerson & Boyd, 1970
	Ear artery	α	6.91*	Bevan, Garstka, Su & Su, 1973
	Intestine	α	7.80	Van Rossum, 1965
	Portal vein	α	5.88*	Hughes & Vane, 1967
	Spleen	α	6.29*	Varma & McCullough, 1969
Rat	Portal vein	α	6.69*	Johansson, Johansson, Ljung & Stage, 1972
	Vas deferens	α	5.92*	Varma & McCullough, 1969
Bovine	Coronary artery	β	5.97*	Kalsner, Frew & Smith, 1975
	Facial artery	β	5.05*	Kalsner, 1978
	Iris sphincter m	β	6.10*	Kalsner, 1978
	Tracheal m.	β	5.83*	Kalsner, 1978
Guinea-pig	Atria	β	6.38*	Westfall & Fleming, 1968
	Tracheal m.	β	5.82	Persson & Johnson, 1979
Human	Colon, longit. m	β	4.74*	Hedges & Turner, 1969
	Ileum, longit. m	β	<5.35*	Hedges & Turner, 1969
	Ileum, circ. m	β	5.00*	Hedges & Turner, 1969
	Lower stomach, longit. m	β	5.27*	Hedges & Turner, 1969
Rabbit	Aorta	β	5.65*	Furchgott, 1954
Rat	Adipose tissue	β	6.48	Brooker & Calvert, 1967
	Uterus	β	5.78*	Levy & Wilkenfeld, 1968

* Calculated values.

† pD_2 is the mean negative log of the molar concentration giving 50% of the maximal response.

does not at all represent activation of a physiologically relevant system of discrete presynaptic β-receptors but interaction with some at present undefined neuronal process. This is clearly reinforced by the data obtained here with the propranolol isomers. Elsewhere, a separate concern has been raised as to the identity of the so-called α-adrenergic system and its postulated role as a negative feedback system (Kalsner, 1979a, b; 1980; Chan & Kalsner, 1979a, b; Kalsner & Chan, 1979).

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