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Lack of presynaptic modulation by isoprenaline of ^{3}H-noradrenaline release from rabbit isolated ear artery

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Summary. The aim of the present investigation was to examine whether or not presynaptic facilitatory β-adrenoceptors are detectable on the postganglionic nerves in the rabbit isolated ear artery. Strips of rabbit central ear artery were incubated with ^{3}H-noradrenaline (10^{-7} mol/l; 30 min or 10^{-6} mol/l; 60 min). Subsequently, they were washed repeatedly with physiological salt solution. The strips were subjected to electrical-field stimulation (S_1-S_8) and the resultant ^{3}H-overflow was determined.

When the ear artery was stimulated with 150 pulses (0.5 ms; 3 Hz; 225 mA), isoprenaline ($10^{-9}-10^{-6}$ mol/l) either alone or in the presence of either rauwolscine (10^{-6} mol/l) or phentolamine (10^{-6} mol/l) did not alter the stimulation-evoked ^{3}H-overflow. This was also the case in the presence of rauwolscine (10^{-6} mol/l) plus either the selective phosphodiesterase inhibitor ICI 63 197 (3×10^{-5} mol/l) or forskolin (10^{-6} mol/l). When the ear artery was stimulated with 300 pulses (1 ms; 5 Hz; 225 mA), isoprenaline had no effect on the stimulation-evoked ^{3}H-overflow. This was also the case when phentolamine (10^{-6} mol/l) was present. Propranolol ($10^{-7}-10^{-5}$ mol/l) did not alter the stimulation-evoked ^{3}H-overflow. In some experiments, the stimulation current was reduced to 175 mA in order to obtain similar reference release (S_3) values despite the presence of rauwolscine (150 pulses; 0.5 ms; 3 Hz). Even then, isoprenaline ($10^{-9}-10^{-6}$ mol/l) did not change stimulation-evoked ^{3}H-overflow. The results suggest that postganglionic sympathetic nerves in rabbit central ear artery do not possess presynaptic facilitatory β-adrenoceptors.

Key words: ^{3}H-Noradrenaline release – Rabbit ear artery – Presynaptic β-adrenoceptors – Isoprenaline – Forskolin

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Introduction

The depolarization-evoked release from postganglionic sympathetic nerves is modulated in many tissues by a facilitatory mechanism which is linked to presynaptic β-adrenoceptors (Majewski 1983; Misu and Kubo 1986; Nedergaard and Abrahamsen 1990). The presence of facilitatory β-adrenoceptors in rabbit ear artery could be revealed only when presynaptic inhibitory α-adrenoceptors were blocked (Majewski and Rand 1981).

Isoprenaline is a non-selective agonist at β-adrenoceptors. This catecholamine enhances the release of noradrenaline in many sympathetically innervated blood vessels (Nedergaard and Abrahamsen 1990), presumably by activation of presynaptic β-adrenoceptors. The aim of the present investigation was to examine if presynaptic β-adrenoceptors are present in the rabbit central ear artery by using isoprenaline as the main pharmacological tool.

A preliminary account of these results was communicated to the British Pharmacological Society (Abrahamsen and Nedergaard 1988).

Materials and methods

Ear artery preparation. Albino rabbits of either sex (1.8–2.6 kg) were killed by a blow to the neck and exsanguinated. Both ears were removed at once and placed in a dissection bath containing physiological salt solution (PSS) at 4° C and aerated with O_2 containing 5% CO_2. The proximal 30 mm of the central ear artery was excised and cleared of fat and connective tissue under a dissection microscope. The ear artery was opened by vertical dissection to form a rectangular strip (approximately 30×3 mm) and then divided into three strips of about equal length. The tissue weight (mean ± SE) was: 3.43 ± 0.07 mg ($n=148$). Each strip was mounted vertically by attaching it to a horizontal plastic rod and a semirigid platinum wire (diameter: 0.4 mm) to a transducer. The strips were placed in jacketed baths filled with PSS (2.0 ml) maintained at 37° C. Each strip was subjected to a resting tension of 1 g. Platinum electrodes (length: 10 mm; diameter: 0.6 mm) were placed in parallel on each side of the strip.

^{3}H-Noradrenaline release. A modification of the general method described by Nedergaard (1980) was used. After suitable mounting

in the tissue baths, the ear artery strips were incubated with ^{3}H-noradrenaline (10^{-7} mol/l) for 30 min. In one series of experiments essentially the same experimental conditions as described by Majewski and Rand (1981) were used. In this case, the strips were incubated for 60 min with ^{3}H-noradrenaline (10^{-6} mol/l). Subsequently, the baths were automatically emptied and refilled with salt solution (2.0 ml) every 2 min for 120 min and then every 5 min for the remainder of the experiment. Each 5-min fraction was collected directly in a counting vial by means of a fraction collector. The ^{3}H-content was assayed by liquid scintillation spectrometry. At the end of each experiment, each strip was exposed to Protosol (0.5 ml; NEN Research Products, Boston, MA, USA) for 16 h at room temperature (approximately 20° C) and the arterial ^{3}H-content was then determined.

The ear arteries were subjected to electrical-field stimulation using a stimulator (model S48, Grass Medical Instruments, Quincy, MA, USA) in connection with a constant-current unit. The vessels were subjected to electrical-field stimulation at various times (min) after onset of wash-out: 75 (S_1) and then every 35 min (S_2-S_8). S_3 (= 100%) was normally used as the initial "control". Each period of stimulation consisted of 150 monophasic pulses (3 Hz; 0.5 ms; 225 mA), unless otherwise remarked. Overflow of tritium was corrected for tissue weight, counting efficiency and specific activity and expressed as a percentage of the total ^{3}H-content in the tissue. The ^{3}H-overflow evoked by field stimulation was calculated by summation of the ^{3}H-overflow in the three fractions which entered in the formation of the peak minus the estimated passive ^{3}H-outflow during this period. The latter was calculated from $[(P_1 + P_2)\ 0.5 + P_3]\ 0.5$, where P_1 and P_2 are the two fractions (corresponding to 10 min) preceding the stimulation-evoked ^{3}H-overflow (S_n) and P_3 (corresponding to 5 min) is the fraction just after S_n. In all experiments the ^{3}H-overflow evoked by stimulation (S_3-S_8) was corrected for the time-dependent changes. This was done by stimulating tissue which was exposed to a drug in parallel with tissue not exposed to the drug. The latter results were used in the correction of the former. Cocaine (3×10^{-5}mol/l) + corticosterone (4×10^{-5} mol/l) were present in all experiments from the onset of wash-out, unless indicated otherwise. Cumulative addition of isoprenaline was done by adding isoprenaline to the bath in increasing concentrations 20 min after $S_n(S_3-S_7)$. Agents (forskolin, ICI 63 197, rauwolscine, propranolol and phentolamine) which might potentially affect the cumulative response to isoprenaline, were added 15 min prior to S_3 and maintained constant for the remainder of the experiment.

Salt solution. The composition of the normal PSS was (in 10^{-3} mol/l): Na^+ 144,1; K^+ 4.9; Ca^{2+} 1.3; Mg^{2+} 1.2; Cl^- 125.5; HCO_3^- 25.0; SO_4^{2-} 1.2; $H_2PO_4^-$ 1.2; and D-(+)-glucose 11.1. The solution also contained calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$, 3×10^{-5} mol/l) and L-(+)-ascorbic acid (10^{-4} mol/l). The solution was maintained at 37° C, equilibrated before and during the experiments with O_2 containing 5% (v/v) CO_2 in the tissue bath and had a pH of 7.4.

Drugs. The following drugs were used: (−)-cocaine hydrochloride (Ph. Eur.); corticosterone (Sigma Chemical Co., St. Louis, MO, USA); dimethylsulfoxide (DMSO; Sigma); forskolin (7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxy-labd-14-ene-11-one; Calbiochem, Behring Diagnostic, La Jolla, CA, USA); ICI 63,197 (2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolol 1,5-a pyrimidine; Imperial Chemical Industries plc; Macclesfield, UK); (−)-isoprenaline (+)-bitartrate (Sigma); (−)-7-^{3}H-(N)-noradrenaline (specific activity 23.1 Ci/mmol; New England Nuclear Chemicals, Dreieich, FRG); phentolamine hydrochloride (Ciba-Geigy AG, Basel, Switzerland); (±)-propranolol hydrochloride (Imperial Chemical Industries plc), and rauwolscine hydrochloride (Carl Roth, Karlsruhe, FRG).

Stock solution were prepared using double-distilled water and stored at 4° C. Corticosterone (8×10^{-2} mol/l) was dissolved in ethanol and prepared fresh daily. Forskolin was dissolved in dimethylsulfoxide (10^{-2} mol/l).

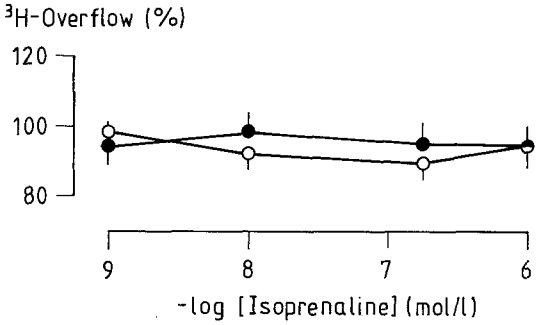

Fig. 1. Effect of isoprenaline on ^{3}H-overflow from rabbit isolated ear artery incubated with ^{3}H-noradrenaline and stimulated at two frequencies. *Ordinate:* mean stimulation-evoked (150 pulses, 225 mA, 0.5 ms) ^{3}H-overflow expressed as a percentage of an initial "control" response (S_3). Tritium overflow (% of tissue tritium) evoked by S_3 was 0.99 ± 0.07 (○) and 1.08 ± 0.12 (●). *Abscissa:* concentration (−log mol/l) of isoprenaline. Frequency (Hz): ●, 1; ○, 3. The salt solution contained cocaine (3×10^{-5} mol/l) plus corticosterone (4×10^{-5} mol/l). *Vertical bars* represent ± SE; $n = 6-8$

Statistics. Results are presented as arithmetic means (± SE). The significance of differences was assessed with Student's *t*-test. A level of probability of $P < 0.05$ was considered significant.

Results

Isoprenaline ($10^{-9}-10^{-6}$ mol/l), phentolamine (10^{-6} mol/l), rauwolscine (10^{-6} mol/l), ICI 63 197 (3×10^{-5} mol/l), forskolin (10^{-6} mol/l) and propranolol ($10^{-8}-10^{-5}$ mol/l) did not alter the passive ^{3}H-outflow.

Isoprenaline ($10^{-9}-10^{-6}$ mol/l) did not alter the stimulation-evoked ^{3}H-overflow from rabbit ear artery strips preincubated with ^{3}H-noradrenaline (Fig. 1). This was the case when the arteries were stimulated at 1 and 3 Hz. In the presence of either phentolamine (10^{-6} mol/l) or rauwolscine (10^{-6} mol/l), non-selective and selective α_2-adrenoceptor antagonists, respectively, isoprenaline ($10^{-9}-10^{-6}$ mol/l) likewise had no effect (Fig. 2).

In interaction experiments with two release-modulating compounds, the first drug administered will by itself modify the release of transmitter, so that the basal conditions are altered, upon which the effect of the second drug is superimposed (Limberger et al. 1988). This was taken into account by decreasing the stimulation current from 225 mA to 175 mA in order to adjust the ^{3}H-overflow evoked by the reference stimulation (S_3). Still, isoprenaline ($10^{-9}-10^{-6}$ mol/l) did not change stimulation-evoked ^{3}H-overflow (Fig. 3).

When the stimulation variables (300 pulses; 1 ms; 5 Hz) were those described by Majewski and Rand (1981), isoprenaline (10^{-7} mol/l) alone or in the presence of phentolamine (10^{-6} mol/l) did not enhance the stimulation-evoked ^{3}H-overflow (Fig. 4).

In the presence of rauwolscine (10^{-6} mol/l) plus either the selective phosphodiesterase inhibitor ICI 63 197 (3×10^{-5} mol/l) or forskolin (10^{-6} mol/l), isoprenaline did not alter the stimulation-evoked ^{3}H-overflow (Fig. 5). Propranolol ($10^{-8}-10^{-5}$ mol/l; $n = 5$) did not

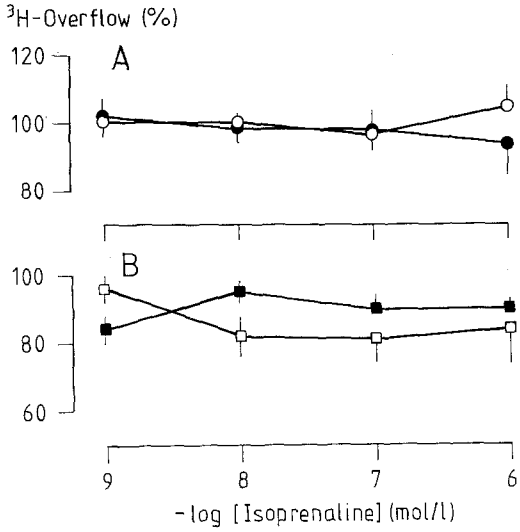

Fig. 2A, B. Effect of isoprenaline in the presence of either rauwolscine or phentolamine on stimulation-evoked ^{3}H-overflow from rabbit isolated ear artery incubated with ^{3}H-noradrenaline. *Ordinate:* mean stimulation-evoked (3 Hz, 150 pulses, 225 mA, 0.5 ms) ^{3}H-overflow expressed as a percentage of an initial "control" response (S_3). Tritium overflow (% of tissue tritium) evoked by S_3 was 0.86 ± 0.07 (○); 2.88 ± 0.17 (●); 1.14 ± 0.09 (□); and 1.49 ± 0.11 (■). *Abscissa:* concentration (−log mol/l) of isoprenaline. **A** ○, Isoprenaline alone; ●, isoprenaline in the presence of rauwolscine (10^{-6} mol/l). **B** □, Isoprenaline alone; ■, isoprenaline in the presence of phentolamine (10^{-6} mol/l). **A, B** The salt solution contained cocaine (3×10^{-5} mol/l) plus corticosterone (4×10^{-5} mol/l). *Vertical bars* represent ± SE; $n = 6-7$

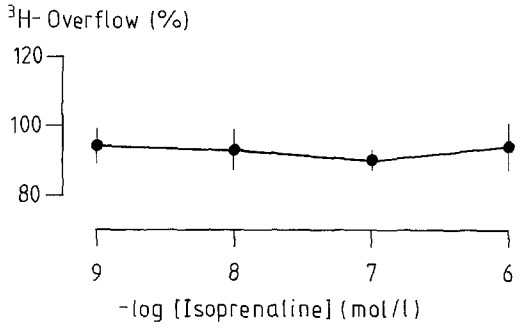

Fig. 3. Effect of isoprenaline in the presence of rauwolscine on stimulation-evoked ^{3}H-overflow from rabbit isolated ear artery incubated with ^{3}H-noradrenaline. *Ordinate:* mean stimulation-evoked (3 Hz, 150 pulses, 175 mA, 0.5 ms) ^{3}H-overflow expressed as a percentage of an initial "control" response (S_3). Tritium overflow (% of tissue tritium) evoked by S_3 was 1.13 ± 0.16. *Abscissa:* concentration (−log mol/l) of isoprenaline. The salt solution contained cocaine (3×10^{-5} mol/l) plus corticosterone (4×10^{-5} mol/l) plus rauwolscine (10^{-6} mol/l). *Vertical bars* represent ± SE, $n = 6$

alter the stimulation-evoked ^{3}H-overflow (results are not shown).

Discussion

The present results do not support the proposal that presynaptic β-adrenoceptors mediate a positive feed-back mechanism facilitating the depolarization-evoked release

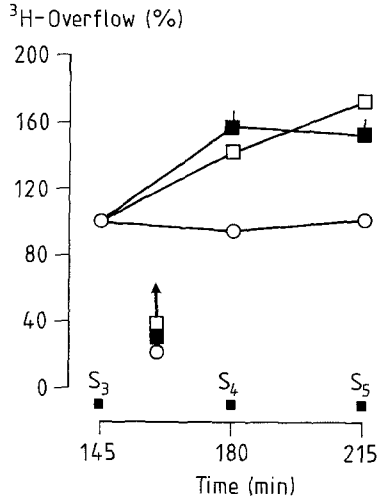

Fig. 4. Time course of the effect of isoprenaline in the presence of phentolamine on stimulation-evoked ^{3}H-overflow from rabbit isolated ear artery incubated with ^{3}H-noradrenaline. *Ordinate:* mean stimulation-evoked ^{3}H-overflow expressed as a percentage of an initial "control" value (S_3). Tritium overflow (% of tissue tritium) evoked by S_3 was 1.10 ± 0.08 (○); 1.80 ± 0.47 (□); and 1.36 ± 0.23 (■). *Abscissa:* time (min) after the onset of wash-out of ^{3}H-noradrenaline. The tissues were incubated with ^{3}H-noradrenaline (10^{-6} mol/l) for 1 h and subjected to stimulation (300 monophasic pulses; 1.0 ms; 5 Hz; 225 mA). Drugs were added as indicated by the *arrow:* ○, isoprenaline (10^{-7} mol/l) alone; □, phentolamine alone; ■, isoprenaline (10^{-7} mol/l) plus phentolamine (10^{-6} mol/l). The salt solution did not contain cocaine plus corticosterone. *Vertical bars* represent ± SE; $n = 5-7$

of transmitter from postganglionic sympathetic neurones in the rabbit ear artery. Thus, isoprenaline did not enhance the stimulation-evoked ^{3}H-overflow from an artery preloaded with ^{3}H-noradrenaline (Fig. 1). This confirms findings with this tissue (Hope et al. 1976; Majewski and Rand 1981), rabbit pulmonary artery (Starke et al. 1975; Johnston and Majewski 1986; Nedergaard 1987), rat portal vein (Enero 1979; Westfall et al. 1984), rat mesenteric artery (Kawasaki et al. 1982), rat renal artery (Kubo et al. 1984), and guinea-pig pulmonary artery (Misu et al. 1984). In contrast, isoprenaline enhanced stimulation-evoked ^{3}H-overflow in rat portal vein (Westfall et al. 1979), rat vena cava (Göthert and Kollecker 1986), rat mesenteric artery (Kubo et al. 1984), rat splenic artery (Kubo et al. 1984), guinea-pig pulmonary artery (Misu et al. 1981; 1983), cat aorta (Langer et al. 1975), dog saphenous vein (Guimarães et al. 1978; Saelens and Williams 1983; Verbeuren et al. 1983), human omental vessels (Stjärne and Brundin 1975; 1976), human digital artery (Stevens et al. 1982), human pulmonary artery (Göthert and Hentrich 1985), and human saphenous vein (Molderings et al. 1988; Verbeuren et al. 1983). High concentrations ($> 10^{-6}$ mol/l) of isoprenaline inhibited the stimulation-evoked ^{3}H-overflow in rabbit pulmonary artery (Starke et al. 1975; Nedergaard 1987).

The positive feedback mechanism for the depolarisation-evoked transmitter release mediated via presynap-

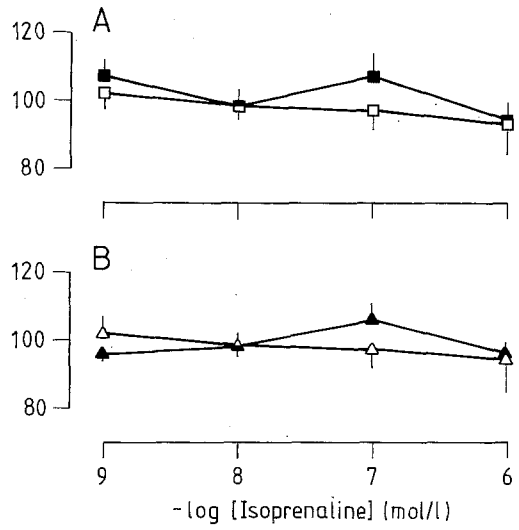

Fig. 5A, B. Influence of rauwolscine, ICI 63 197 and forskolin on the effect of isoprenaline on stimulation-evoked ^{3}H-overflow from rabbit isolated ear artery incubated with ^{3}H-noradrenaline. *Ordinate:* mean stimulation-evoked (3 Hz, 150 pulses, 225 mA, 0.5 ms) ^{3}H-overflow expressed as a percentage of an initial "control" response (S_3). Tritium overflow (% of tissue tritium) evoked by S_3 (in the presence of rauwolscine) was 2.88 ± 0.17 (□); 2.29 ± 0.39 (■); 2.88 ± 0.17 (△); and 3.89 ± 0.35 (▲). *Abscissa:* concentration (−log mol/l) of isoprenaline. **A** □, isoprenaline alone; ■, isoprenaline in the presence of ICI 63 197 (3×10^{-5} mol/l). **B** △, Isoprenaline alone; ▲, isoprenaline in the presence of forskolin (10^{-6} mol/l). **A, B.** The salt solution contained rauwolscine (10^{-6} mol/l) plus cocaine (3×10^{-5} mol/l) plus corticosterone (4×10^{-5} mol/l). *Vertical bars* represent ± SE, $n = 6-7$

tic β-adrenoceptors is supposed to be initiated by low biophase concentration of endogenous transmitter. This view is based on the finding that the facilitation of transmitter release by isoprenaline in cat aorta was inversely related to the stimulation frequency used (Langer et al. 1975). The present results show that even at two low frequencies (1 and 3 Hz), isoprenaline did not alter the stimulation-evoked ^{3}H-overflow. This was also the case with adrenaline (Abrahamsen and Nedergaard 1991). This indicates that the positive feedback mechanism is not present in the ear artery.

It has been proposed that there is an inhibitory link between presynaptic β-adrenoceptor systems and presynaptic α-adrenoceptors which may explain why in some tissues facilitatory presynaptic β-adrenoceptors could not be demonstrated (Majewski 1983; Nedergaard and Abrahamsen 1990). According to this proposal, blockade of presynaptic α_2-adrenoceptors should unmask the presence of β-adrenoceptors, if any. Thus, only in the presence of phentolamine, did isoprenaline have a facilitatory effect in the rabbit pulmonary artery (Johnston and Majewski 1986), and the rabbit ear artery (Majewski and Rand 1981). However, in the present study, isoprenaline did not enhance the stimulation-evoked ^{3}H-overflow in either the presence of rauwolscine or phentolamine, selective α_2- and non-selective adrenoceptor antagonists, respectively (Fig. 2). Likewise, adrenaline did not enhance stimulation-evoked ^{3}H-overflow (Abrahamsen and Nedergaard 1991). Even when the stimulation variables (300 pulses; 1 ms; 5 Hz) were the same as those used by Majewski and Rand (1981), isoprenaline did not cause an enhancement (Fig. 4).

It has been suggested that presynaptic β-adrenoceptors in blood vessels are linked to cyclic AMP which is involved in the regulation of action potential-induced noradrenaline release (Göthert and Hentrich 1984). Thus, in the presence of ICI 63 197, a reputed selective inhibitor of cyclic AMP phosphodiesterase, isoprenaline enhanced the stimulation-evoked ^{3}H-overflow from rabbit pulmonary artery preloaded with ^{3}H-noradrenaline (Johnston and Majewski 1986). In the rabbit ear artery, isoprenaline plus ICI 63 197 did not alter the stimulation-evoked ^{3}H-overflow even though presynaptic inhibitory α_2-adrenoceptors were inhibited by rauwolscine (Fig. 5).

Forskolin activates adenylate cyclase, probably by acting directly on the catalytic subunit of the enzyme (Seamon and Daly 1986). Forskolin potentiated the facilitatory effect of isoprenaline on the stimulation-evoked release of ^{3}H-noradrenaline (Hentrich et al. 1985). We found, however, that isoprenaline in the presence of forskolin did not alter the stimulation-evoked ^{3}H-overflow (Fig. 5). The present results (Fig. 5) obtained with tools which probably increase intraneuronal cyclic AMP content and thereby potentially optimize the experimental conditions for demonstrating presynaptic β-adrenoceptors, indicate that these receptors are not present at the sympathetic nerve endings.

β-Adrenoceptor antagonists should decrease the stimulation-evoked ^{3}H-noradrenaline release if neurogenic noradrenaline plays a role in the positive feed-back loop (Nedergaard and Abrahamsen 1990). We found that propranolol did not alter the stimulation-evoked ^{3}H-overflow which indicates either that noradrenaline does not activate presynaptic β-adrenoceptors or that these receptors are not present in the rabbit ear artery.

The effectiveness of presynaptic ligands in modulating the release of noradrenaline depends, inter alia, on the magnitude of the release *before* addition of the ligand. In general, the modulation is weak when the release before the addition of the ligand is high, due – for instance – to stimulation at high current strength (Limberger et al. 1988). We therefore reduced the current strength of stimulation in order to obtain a similar release (S_3) value despite the initial modulating agent rauwolscine. The result was that the lack of effect of isoprenaline when administered in the presence of rauwolscine could not be explained by the increase in release per se that rauwolscine caused (Fig. 3).

The present study demonstrates that isoprenaline does not enhance stimulation-evoked transmitter release in rabbit ear artery. This indicates that presynaptic facilitatory β-adrenoceptors are not present in this tissue.

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