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PRE- AND POSTSYNAPTIC α-ADRENOCEPTOR BLOCKING ACTIVITY OF RAUBASINE IN THE RAT VAS DEFERENS

PATRICIA DEMICHEL, PATRICK GOMOND & JACQUES ROQUEBERT

Laboratory of Pharmacology, U.E.R. de Pharmacie, 3 Place de la Victoire, 33000 Bordeaux, France.

1 The actions of raubasine, yohimbine and corynanthine at pre- and postsynaptic α-adrenoceptors were studied in the rat vas deferens.

2 Low frequency electrical stimulation of the isolated vas deferens of the rat produced regular contractions that were inhibited by low concentrations of clonidine. This inhibition was presynaptic in origin and involved α-adrenoceptors.

3 Presynaptic α-adrenoceptor antagonist activity was assessed by studying the effect of increasing antagonist concentrations on cumulative clonidine dose-response curves on the stimulated vas deferens.

4 Postsynaptic α-adrenoceptor antagonist activity in the isolated vas deferens was assessed by comparing control cumulative noradrenaline dose-response curves in the absence and in the presence of increasing concentrations of antagonists.

5 The results indicate that raubasine and corynanthine preferentially block postsynaptic α-adrenoceptors. Yohimbine is more potent in blocking pre- than postsynaptic α-adrenoceptors. The ratio of the pre/postsynaptic potency declines in the order yohimbine > raubasine > corynanthine.

Introduction

The differentiation between pre- and postsynaptic α-adrenceptors is now widely accepted (for reviews see Langer, 1977; Starke, 1977). The terminology α_2 for pre- and α_1 for postsynaptic α-adrenoceptors was originally suggested by Langer (1974) and this concept was generalized by Berthelsen & Pettinger (1977). The two types of α-adrenoceptors differ in their selectivity for agonists and antagonists (Starke, 1972; Dubocovitch & Langer, 1974; Starke, Endo & Taube, 1975; Drew, 1976; Docherty, McDonald & McGrath, 1979; Timmermans, Kwa & Van Zwieten, 1979; Weitzell, Tanaka & Starke, 1979; Docherty & McGrath, 1980; Kobinger & Pichler, 1980).

Raubasine (Δ-yohimbine, ajmalicine) was isolated originally from *Rauwolfia serpentina* by Popelak, Kaiser & Spingler (1953) and subsequently from *Vinca rosea* (Kohlmunzer & Krupinska, 1960). The adrenolytic and sympatholytic properties of raubasine have been described by many authors. Raubasine reverses the hypertensive effects of adrenaline (Achelis & Kroneberg, 1953; Kroneberg & Achelis, 1954; Schmitt & Gonnard, 1957; Kroneberg, 1958), decreases those of noradrenaline (Schmitt & Gonnard, 1957), diminishes the contractile response of the nictitating membrane of the cat elicited by nerve stimulation and inhibits the response of muscle to exogenous adrenaline (Schmitt & Gonnard, 1957). Raubasine antagonizes the effects of adrenaline in the rabbit uterus (Raymond-Hamet & Rothlin, 1960), the guinea-pig seminal vesicle and the rabbit intestine *in vitro* (Kroneberg, 1958).

The vas deferens is an organ in which motor transmission is thought to be modulated by an inhibitory presynaptic α-adrenoreceptor. The twitch response of the vas deferens to low frequency nerve stimulation is reduced by administering an exogenous α-adrenoceptor agonist (Ambache & Zar, 1971; Jenkins, Marshall & Nasmyth, 1976). This effect is accompanied by a reduction in the release of [^{3}H]-noradrenaline from sympathetic nerves (Vizi, Somogyi, Hadhazy & Knoll, 1973). The inhibitory effect of the agonist on the twitch response and on the release of [^{3}H]-noradrenaline is prevented by phentolamine (Vizi, *et al.*, 1973).

The present experiments were undertaken to determine the pre- and postsynaptic α-blocking activities of raubasine in the rat vas deferens. The results were compared to those obtained with yohimbine, which preferentially blocks the α_2-receptor, and with corynanthine, which primarily blocks the α_1-receptor (Weitzell, *et al.*, 1979).

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Methods

Isolated vas deferens of rat

Vasa deferentia were removed from Wistar rats (230 ± 20 g) and suspended under a preload of 0.5 g in a 20 ml muscle chamber containing Krebs solution at 37°C and gassed with 95% O_2 and 5% CO_2. The composition of the Krebs solution was (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 0.6, $NaHCO_3$ 25, KH_2PO_4 1.2 and glucose 11.1.

After a 30 min stabilization period, contractions were measured with an isotonic myograph transducer and recorded on a chart recorder.

Postsynaptic activity

Noradrenaline produces contractions of the rat vas deferens by stimulating the postsynaptic α-adrenoceptors. Cumulative dose-response curves (Van Rossum, 1963) were obtained by adding increasing amounts of noradrenaline to the incubation medium every 45 s. Two complete cumulative dose-response curves for noradrenaline were obtained with a 15 min interval between the two curves. After establishing the agonist-induced contractile response, a given quantity of antagonist was introduced into the chamber 5 min before a new cumulative curve was established for the agonist. Results are expressed as percentages of the maximal contractions.

The reversibility of the eventual inhibition exerted by one of the substances was systematically verified by establishing a control curve between each trial. Five isolated organs were used for each antagonist concentration.

Presynaptic activity

The experimental procedure used to determine quantitatively the effects of the antagonists at presynaptic α-adrenoceptors was similar to that described by Drew (1977).

Platinum electrodes were placed near the top and bottom of the tissue and the intramural nerves of the vas deferens were stimulated by square wave pulses: 2 ms duration, 30 V, 0.1 Hz. The twitch response to field stimulation declined steadily and then became stable. When the twitches became constant, increasing concentrations of clonidine were added to the bathing fluid every 3 min without intermediate washing. The inhibitory effect of each concentration on the twitch response was expressed as a percentage inhibition of the maximal contraction. Thus, it was possible to construct cumulative dose-response curves for clonidine. After producing two successive and comparable control curves (clonidine alone) the sensitivity of the preparation towards clonidine was again determined after 10 min of contact with an antagonist.

Five isolated organs were used at each antagonist concentration.

Expression of results

The types of interaction between agonists and antagonists can be deduced as a first approximation from the quantitative study of a series of curves (Van Rossum, 1963). When competitive antagonism is suspected, the results are confirmed by the weighted regression straight line test for log (x−1) against log (antagonist concentration) described by Arunlakshana & Schild (1959). x = Ab/Ao, the ratio of the agonist concentration required to obtain the same fraction of the maximum effect in the presence (Ab) or absence (Ao) of the antagonist. The slope of this straight line was compared to the value 1 with the Student-Fischer *t* test (Gremy & Salomon, 1969). The pA_2 parameters of conventional affinity in the case of competitive antagonism were determined as described by Van Rossum (1963) and by Arunlakshana & Schild (1959). The affinity of agonists were expressed by their pD_2 values, determined by the method of Ariëns & Van Rossum (1957) and Van Rossum (1963).

Drugs

(−)-Noradrenaline bitartrate (Koch-Light), yohimbine hydrochloride (Sigma), corynanthine hydrochloride (Sigma), clonidine hydrochloride (Boehringer Ingelheim), guanethidine sulphate (Ciba), hexamethonium bromide (Merck) and cocaine hydrochloride (Cooper) were dissolved in Krebs solution, except for raubasine, (P. Fabre Labs) which was dissolved in 1% tartaric acid solution (35 mg raubasine, 10 ml tartaric acid solution) and further diluted with the Krebs solution mentioned above.

Statistical analyses

Statistical analyses were performed with Student's *t* test.

Results

Antagonist activity at postsynaptic α-adrenoceptors

The effects of raubasine, yohimbine and corynanthine on the cumulative dose-response curves of noradrenaline are illustrated in Figure 1. In the presence of these drugs (10^{-7}–10^{-5} M), noradrenaline dose-response curves were shifted to the right in

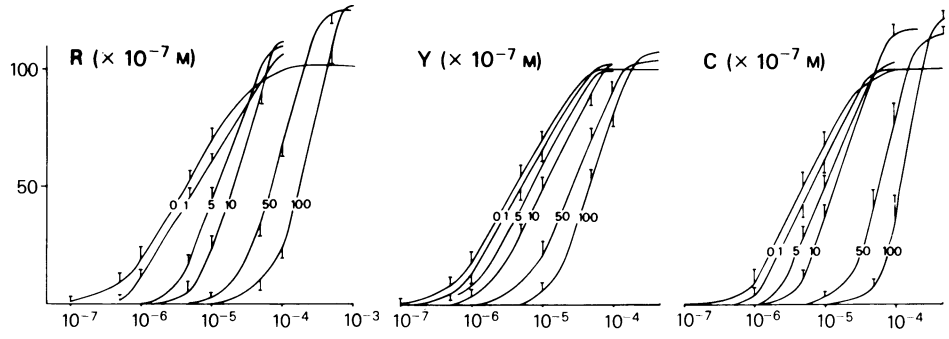

Figure 1 Cumulative dose-response curves to noradrenaline in the rat vas deferens in the presence of raubasine (R), yohimbine (Y) or corynanthine (C). Ordinate scale: % of maximal noradrenaline response in the absence of (R), (Y) or (C). Abscissa scale: − log molar concentration of noradrenaline. Each point represents the mean of 5 experiments; vertical lines show s.e.mean.

parallel, without the maximal contraction being depressed.

However, under our experimental conditions the maximum noradrenaline response increased slightly but steadily in the presence of raubasine and corynanthine but not in the presence of yohimbine. This effect has already been described for phentolamine (Barnett, Greenhouse & Taber, 1968), yohimbine, piperoxane and tolazoline (Jurkiewicz & Jurkiewicz, 1976). The increase in the maximum response to noradrenaline induced by α-adrenoceptor blockers was dependent on the time of incubation, on the antagonist and on the initial amplitude of the responses to the agonist and results from events occurring after drug-receptor interaction (Jurkiewicz & Jurkiewicz, 1976). In the present work, potentiation appears not to change significantly the adrenoceptor blocking activity of raubasine, yohimbine and corynanthine. The pA_2 values were 6.50 ± 0.04 for raubasine, 6.32 ± 0.06 for corynanthine and 6.10 ± 0.01 for yohimbine. There was always a linear relationship between log (x−1) for noradrenaline and log molar concentration of antagonist (Arunlakshana & Schild, 1959) and the slope of the regression line was not significantly different from 1 (Table 1). The effects of these three substances were easily reversed by adding fresh perfusion fluid.

Experiments were performed after blockade of neuronal uptake with cocaine (Iversen, 1967). At the concentration used ($3 + 10^{-6}$ M), cocaine had no significant influence on the maximum response to noradrenaline, although it induced a shift of the dose-response curve to the left. After cocaine treatment raubasine, yohimbine and corynanthine shifted noradrenaline response curves to the right in parallel, without increasing the maximal contraction. The pA_2 values obtained under such conditions were 6.75 ± 0.02 for raubasine, 6.57 ± 0.05 for yohimbine and 6.62 ± 0.04 for corynanthine. The relation between the increment of antagonist concentration and the shift in dose-response curves was analysed by the Schild plot (Arunlakshana & Schild, 1959), according to which a slope of 1 is expected for the regression line. Such a slope was obtained with the antagonists studied (Table 1).

Table 1 Drug antagonism at postsynaptic α-adrenoceptors of the rat vas deferens: pD_2 values were determined according to Van Rossum (1963), pA_2 values and slope of regression were calculated from Schild plots (Arunlakshana & Schild, 1959)

	Drug parameter			
	Without cocaine	*Slope*	*With cocaine*	*Slope*
Agonist				
Noradrenaline	$pD_2 = 5.31 \pm 0.1$		$pD_2 = 6.47 \pm 0.2$	
Antagonists				
Raubasine	$pA_2 = 6.57 \pm 0.04$	0.96 ± 0.02	$pA_2 = 6.76 \pm 0.02$	1.019 ± 0.01
Yohimbine	$pA_2 = 6.21 \pm 0.03$	0.82 ± 0.06	$pA_2 = 6.62 \pm 0.05$	0.95 ± 0.02
Corynanthine	$pA_2 = 6.34 \pm 0.06$	0.98 ± 0.18	$pA_2 = 6.64 \pm 0.04$	0.96 ± 0.02

$n = 5$

Antagonist activity at presynaptic α-adrenoceptors

Presynaptic α-agonist activity Low frequency (0.1 Hz) electrical stimulation of the rat isolated vas deferens produced contractions or 'twitches' which declined steadily during the first 10 min, probably because noradrenaline released from noradrenergic nerves regulates its own release by a negative feedback mechanism involving inhibitory presynaptic α-adrenoceptors (Langer, 1974). Constant responses were obtained about 15–20 min after the start of the experiment. The twitch responses were abolished by guanethidine (10^{-7} M), indicating that they resulted from nerve stimulation but were unaffected by the ganglion blocking drug, hexamethonium (10^{-6} M), suggesting that they arose from post-ganglionic nerve stimulation. Clonidine caused a dose-dependent inhibition of the twitch response; the pD_2 value (Van Rossum, 1963) was 8.60 ± 0.05. The inhibitory effect of clonidine was reversed by phentolamine (10^{-7} M). In contrast, the guanethidine-induced inhibition of the twitch response was not affected by phentolamine. This suggests that clonidine inhibits the twitch response by a mechanism involving presynaptic α-adrenoceptors. The inhibitory effect of guanethidine was not modified by raubasine (5×10^{-7}–5×10^{-5} M).

Effects of α-adrenoceptor antagonists on the twitch response Both raubasine (10^{-6}–5×10^{-5} M) and yohimbine (10^{-8}–10^{-7} M) enhanced the twitch response to nerve stimulation. Corynanthine at concentrations up to 10^{-6} M had little effect on the twitch response but increased these responses at concentrations from 10^{-5}–5×10^{-5} M. The order of potency for this effect is raubasine > yohimbine > corynanthine. A similar effect has been described for several other α-blockers, including phentolamine, piperoxan, thymoxamine (Drew, 1977), azapetine (McGrath, 1978), WB 4101 (Butler & Jenkinson, 1978), yohimbine (Brown, McGrath & Summers, 1979). It has been suggested (Vizi, *et al.*, 1973) that this effect results from blockade of the presynaptic α-inhibitory feed-back system normally activated by endogenously released noradrenaline. This mechanism is unlikely since there was no correlation between the potentiating effects of the α-antagonists on the twitch response and their ability to block presynaptic α-receptors. Drew (1977), and Brown, *et al.* (1979) suggested a postsynaptic site of action unrelated to α-adrenoceptor blockade.

Interactions between clonidine and α-adrenoceptor antagonists

In this experiment, the influence of the antagonist on the twitches was eliminated graphically by expressing each set of responses as a percentage of its own maximum.

Raubasine (5×10^{-7}–5×10^{-5} M), yohimbine (10^{-9}–10^{-7} M) and corynanthine (10^{-6}–5×10^{-5} M) produced parallel concentration-dependent shifts of the clonidine dose-response curve to the right (Figure 2). The pA_2 values (Van Rossum, 1963) were 6.02 ± 0.07 for raubasine, 8.26 ± 0.02 for yohimbine and 4.99 ± 0.07 for corynanthine. Schild plots (Arunlakshana & Schild, 1959) gave linear regressions in every case (Figure 3). The pA_2 values and slopes of the regression lines are given in Table 2.

The antagonism of the clonidine-induced inhibition by α-adrenoceptor blocking agents does not appear to be a physiological antagonism of the action of clonidine, since the inhibition produced by the neuronal blocking agent, guanethidine, is not reversed by phentolamine, yohimbine (Doxey, Smith & Walker, 1977) and raubasine.

Ratio of pre- to postsynaptic potency

The data obtained with these two preparations en-

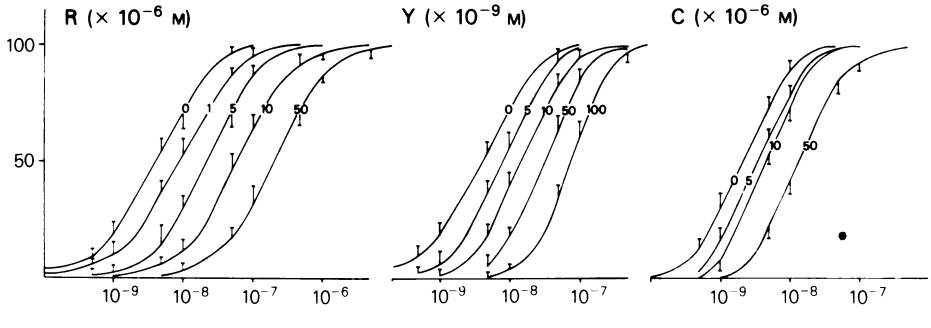

Figure 2 Antagonism of the twitch-inhibitory effect of clonidine by raubasine (R), yohimbine (Y) or corynanthine (C) in electrically stimulated rat vas deferens (0.1 Hz, 30 V, 2 ms). Ordinate scale: % of maximal inhibition. Abscissa scale: – log molar concentration of clonidine. Each point is mean of 5 experiments; vertical lines show s.e.mean.

Table 2 Drug antagonism at presynaptic α-adrenoceptors of the rat vas deferens after intramural nerve stimulation: pD_2 values were determined according to the method of Van Rossum (1963), pA_2 values and slope of regression lines were calculated from Schild plots (Arunlakshana & Schild, 1959)

Agonist	*Antagonist*	*Drug parameter*	*Slope*
Clonidine		$pD_2 = 8.53 \pm 0.15$	
	Raubasine	$pA_2 = 6.02 \pm 0.07$	1.02 ± 0.06
	Yohimbine	$pA_2 = 8.26 \pm 0.08$	0.98 ± 0.07
	Corynanthine	$pA_2 = 4.99 \pm 0.07$	1.04 ± 0.06

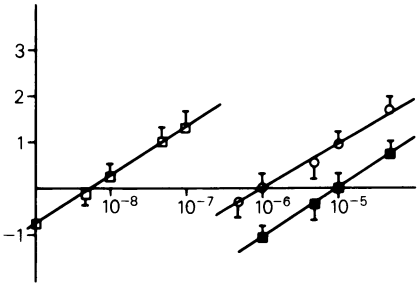

Figure 3 Schild plot of the results shown in Figure 2 for the raubasine (○), yohimbine (□) and corynanthine (■) antagonism of clonidine-induced inhibition of contraction in electrically stimulated rat vas deferens. Ordinate scale: log (x − 1) where x = ratio of the agonist concentration required to obtain the same fraction of the maximum effect in the presence or absence of the antagonist. Abscissa scale: − log molar concentration of antagonist. Each point is the mean 5 experiments; vertical lines show s.e.mean.

abled the ratio of pre- to postsynaptic potency to be determined (Table 3).

Discussion

The study of the action of raubasine, yohimbine and corynanthine on the response of the isolated vas deferens to noradrenaline shows that each of these drugs produces a parallel shift of the dose-response curves to the right with an increase in the maximal contraction. In the presence of cocaine, which blocks the neuronal uptake process, the dose-response curves were shifted to the right without increasing the maximal contraction to noradrenaline. According to occupation theory (Ariens, 1964) log-dose response curves of the agonist can be shifted to the right by reversible competitive antagonists following Schild's equation (Arunlakshana & Schild, 1959). The results of this analysis are indicated in Table 1. The slope of the regression lines are not significantly different from 1. This indicates that the antagonisms studied may be considered to be competitive, at least in the rat vas deferens. The differences observed between the three drugs are not significant.

In the experiments with transmurally stimulated rat vas deferens the α-antagonists caused parallel shifts of the clonidine dose-response curves to the right, suggesting a competitive antagonism. Schild plot regressions were linear and in all cases gave slopes not significantly different from 1 (Table 2). The pA_2 value of yohimbine was significantly different from that of raubasine ($P < 0.01$) and corynanthine ($P < 0.01$). The pA_2 value of raubasine was significantly different from that of corynanthine ($P < 0.01$).

In the experiments comparing the relative potencies of α-adrenoceptor blocking agents at presynaptic and postsynaptic α-adrenoceptors, it was clear that the structural requirements for each receptor were different. The pA_2 of yohimbine towards clonidine was significantly greater ($P < 0.01$) than its value toward noradrenaline. Yohimbine preferentially blocked presynaptic α-adrenoceptors. Corynanthine acted preferentially at the postsynaptic α-adrenoceptor and the difference between its pA_2 values towards noradrenaline and clonidine was significant ($P < 0.01$). These results agree with those of

Table 3 Antagonist potency at pre- and postsynaptic α-adrenoceptors, pA_2 values were calculated from Schild plots and then converted to their respective molar concentrations: the pre-/postsynaptic ratios were calculated from these concentrations

Compound	*Postsynaptic molar concentration*	*Presynaptic molar concentration*	*Ratio pre/post*
Raubasine	2.69×10^{-7}	9.54×10^{-7}	0.281
Yohimbine	6.16×10^{-7}	5.49×10^{-9}	112
Corynanthine	4.57×10^{-7}	1.02×10^{-5}	0.044

Weitzell, *et al.* (1979). Raubasine was also more active at postsynaptic α-adrenoceptors than presynaptic receptors and the difference between its pA_2 towards clonidine and noradrenaline was significant ($P < 0.01$). Raubasine, however, had more affinity for presynaptic α-adrenoceptors than corynanthine. In the rat vas deferens the ratio of presynaptic blocking potency/postsynaptic blocking potency declines in the order yohimbine > raubasine > corynanthine.

Correspondence to J.B., please

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