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AN ANALYSIS OF SOME FACTORS INFLUENCING α-ADRENOCEPTOR FEED-BACK AT THE SYMPATHETIC JUNCTION IN THE RAT HEART

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1 The effects of the selective prejunctional α-adrenoceptor antagonist, yohimbine, on the cardioacceleration responses to sympathetic stimulation were examined in the pithed rat.

2 Yohimbine reversed the inhibitory effects of the α-adrenoceptor agonist, clonidine, on the stimulation-induced tachycardia.

3 Yohimbine failed to potentiate significantly responses to stimulation in the absence of clonidine when stimulation was applied at the optimal level for cardiac responses (C6-T1).

4 When the pithing rod electrode was moved to T2-T6, cardioaccelerator responses were smaller and yohimbine produced potentiation at frequencies of $\geqslant 1$ Hz. This potentiation was prejunctional since responses to exogenous noradrenaline (NA) were not increased by yohimbine.

5 In the presence of cocaine, potentiation by yohimbine could be shown at the lower frequency of 0.1 Hz.

6 The possible physiological significance of a negative feed-back effect of noradrenaline on cardiac sympathetic nerves is discussed.

Introduction

The cardioacceleration response of rat heart to sympathetic nerve stimulation can be inhibited by agonist drugs, such as clonidine, which act at prejunctional α-adrenoceptors on the nerve terminals to reduce the output of noradrenaline (Armstrong & Boura, 1973; Drew, 1976; Doxey, 1977). This inhibitory effect can be reversed or prevented by selective antagonists of these prejunctional α-adrenoceptors e.g. yohimbine (Starke, Borowski & Endo, 1975; Drew, 1976). It has been demonstrated in a number of tissues *in vitro* that such antagonists can increase the stimulation-induced outflow of noradrenaline from sympathetic nerves, suggesting an endogenous feed-back process in which noradrenaline inhibits its own further release by acting at these prejunctional α-adrenoceptors (see Langer, 1974; Starke, 1977).

If this process operates under physiological conditions, then the response of the postjunctional effector should be potentiated by an agent which is a selective prejunctional α-adrenoceptor antagonist. It has recently been demonstrated in principle that the sympathetic cardioaccelerator response *in situ* in the pithed rat can be potentiated by yohimbine or phentolamine (Docherty & McGrath, 1977a; Doxey, 1977). We have now investigated the conditions under which yohimbine may potentiate this sympathetic transmitter process.

We first determined the dose of yohimbine which was necessary to antagonize the prejunctional effects of clonidine. The effects of these doses of yohimbine on transmission were examined to ascertain whether an endogenous feed-back could be uncovered. In the course of the investigation, two major factors affecting the demonstration of endogenous feed-back emerged. (1) With supramaximal stimulation of the accelerans nerve, the postjunctional response i.e. tachycardia, became maximal at the frequency range of $\geqslant 1$ Hz at which feed-back might be expected, thus eliminating the possibility of potentiation. (2) The operation of the neuronal reuptake of noradrenaline modified the frequency range at which feed-back occurred.

This paper therefore concentrates on employing (1) submaximal and supramaximal stimuli and (2) drugs which block the neuronal uptake of noradrenaline, in order to determine the conditions necessary to demonstrate α-adrenoceptor-mediated feed-back.

A preliminary account of this work has been published (Docherty & McGrath, 1977a).

Methods

Male Wistar rats (250 to 300 g) were pithed by the method of Gillespie, MacLaren & Pollock (1970) and

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ventilated with 100% O_2, 1 ml/100 g per beat, at a rate of 60/min (Clanachan & McGrath, 1976). Heart rate was extracted from carotid arterial pressure by means of a Devices instantaneous ratemeter. The right jugular vein was cannulated for drug injections.

Cardiac sympathetic nerve stimulation

In all experiments the 10 mm tip of the pithing rod was used as an electrode, with pulses of 0.05 ms and supramaximal voltage. With this short pulse duration no neuromuscular blocking agent was necessary since skeletal muscle twitching was acceptably small, allowing drug-free control responses (Docherty & McGrath, 1978). Two different electrode positions were used to stimulate the sympathetic outflow to the heart; maximal responses, C6-T1; submaximal responses, T2-T6.

In one group of experiments involving nerve stimulation, reproducible control responses were obtained before injection of the test drug (a) at varying frequencies with a fixed number of pulses or (b) at a fixed frequency with varying numbers of pulses. Following injection of the test drug, stimulation was repeated within as short a period as possible after recovery of heart rate to control levels. In addition, the order of stimulus trains of different frequency or pulse number was randomized to rule out error due to a time-dependent decline in the effect of the test drug.

In another set of experiments the test drugs were injected during the maintained response to repetitive cardioaccelerator nerve stimulation at 0.1 Hz, and stimulation was continued until the response to the drug reached a steady level. In some cases the response to the test drug was then reversed by an antagonist drug.

In experiments where cocaine was injected before the test drug, control responses were first obtained in the presence of cocaine. To rule out any effect due to a time-dependent decline in the blockade by cocaine of neuronal noradrenaline uptake, a high dose was normally used (3.3 mg/kg) (Docherty & McGrath, 1978).

Adrenalectomized rats

Some experiments were carried out in rats which had been adrenalectomized, via a mid-line incision in the abdomen, after pithing. In control rats, adrenal responses were only found when stimulating at T2-T6 and even these were only significant at frequencies of ≥ 5 Hz (Docherty & McGrath, 1978). Adrenalectomized rats were therefore used when stimulating under the latter conditions.

Effects on the response to noradrenaline

To assess whether the effects of test drugs were pre- or postsynaptic in origin, their effects on the cardiac response to intravenous noradrenaline (200 ng/kg) were examined.

Drugs used were clonidine hydrochloride (Boehringer Ingelheim), cocaine hydrochloride (Cockburns), noradrenaline bitartrate (Koch-Light) and yohimbine hydrochloride (Sigma).

Drugs were dissolved in saline (0.9% w/v). Doses quoted are in terms of the salt. Drugs were injected in a volume of 1 ml/kg intravenously, and washed in with 1 ml/kg saline. Control saline injections were of 2 ml/kg.

Results

Reversal of the effects of clonidine by yohimbine

Continuous stimulation of cardioaccelerator nerves (C6-T1) at 0.1 Hz produced a sustained elevation of heart rate of 65.2 $\pm$ 5.3 min^{-1} ($n = 6$). At this point clonidine (100 μg/kg) was injected and produced a rapid fall in heart rate of 56 min^{-1} which settled to a maintained decrease in heart rate of 51.3 $\pm$ 8.2 min^{-1} ($n = 6$) below the pre-injection level in approximately 3 min. When the baseline was reached, yohimbine (100 μg/kg) was injected and partially reversed the effects of clonidine by 12.3 $\pm$ 2.2 min^{-1} ($n = 6$) within approximately 3 min. A subsequent dose of yohimbine (1 mg/kg) produced a further reversal of 30.0 $\pm$ 5.8 min^{-1} ($n = 6$) in approximately 6 min (Figure 1a). In rats not given yohimbine there was no recovery at all from the effects of this dose of clonidine within the same time.

In the presence of cocaine (3.3 mg/kg), continuous cardioaccelerator stimulation (C6-T1) at 0.1 Hz produced a sustained cardioacceleration of 95.8 $\pm$ 13.6 min^{-1} ($n = 4$). When injected during stimulation, clonidine (100 μg/kg) caused a decrease in heart rate of 103.0 $\pm$ 10.6 min^{-1} ($n = 4$) in 3 min. Yohimbine (100 μg/kg) reversed this inhibition by 36.5 $\pm$ 6.0 min^{-1} ($n = 4$) in 4 min, and yohimbine (1 mg/kg) reversed it by a further 43.5 $\pm$ 9.0 min^{-1} in 6 min ($n = 4$) (Figure 1b).

Effects of yohimbine on the cardioacceleration response

Maximal stimuli In the absence of clonidine, yohimbine (100 μg/kg) failed to cause an elevation of heart rate when injected during continuous cardioaccelerator stimulation at 0.1 Hz, and yohimbine (1 mg/kg) in fact produced a marked inhibition of the response which recovered slowly (Figure 2a, b). Control saline injections produced only a transient fall in heart

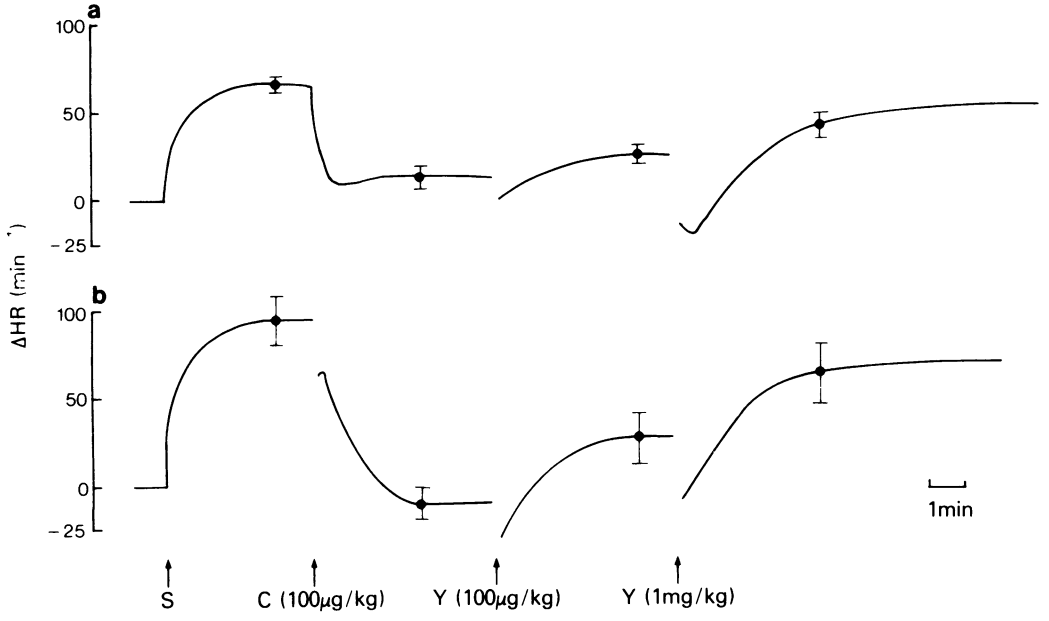

Figure 1 Reversal by yohimbine of the effects of clonidine during 0.1 Hz continuous cardioaccelerator stimulation: (a) control, (b) in the presence of cocaine (3.3 mg/kg). Stimulation (C6-T1) started at S, clonidine was injected at C and yohimbine at Y. The graph was constructed from the means of data taken every 10 s for the first min after the start of stimulation or administration of a drug and thereafter at 1 min intervals. For the sake of clarity symbols with error bars (s.e. of mean) are only shown at certain points. (a) $n = 6$, (b) $n = 4$.

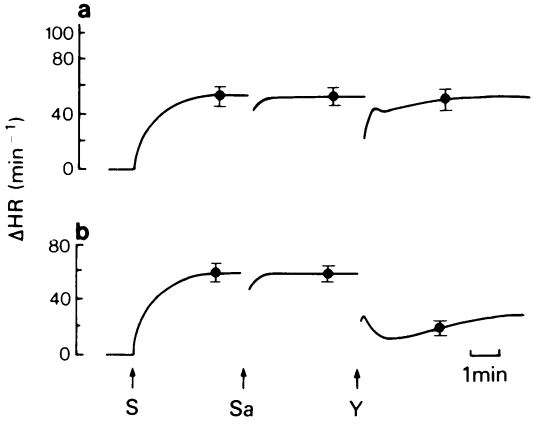

Figure 2 Effects of yohimbine on the cardioacceleration response to 0.1 Hz continuous stimulation (C6-T1). Stimulation started at S, saline was injected at Sa and yohimbine at Y 100 μg/kg in (a) or 1 mg/kg in (b). The graph was constructed as for Figure 1. Vertical bars represent s.e. mean. (a) $n = 7$, (b) $n = 5$.

rate. Even in the absence of stimulation, yohimbine (1 mg/kg) caused a depression of heart rate, with recovery in 1 to 5 min. At 0.1 Hz endogenous feed-back could not, therefore, be demonstrated.

With higher stimulus frequencies of ≥ 0.5 Hz, when stimulating cardioaccelerator nerves optimally (C6-T1), the heart rate became maximal so that potentiation could not be demonstrated. To avoid this, the pithing rod electrode was moved to T2-T6 so as to stimulate fewer cardioaccelerator fibres, and hence obtain submaximal responses at high frequencies (Figure 3).

Submaximal stimuli The effects of yohimbine (100 μg/ kg and 1 mg/kg) on the cardioacceleration evoked by stimulation (T2-T6) at 0.5 to 5 Hz were tested. Significant potentiation was obtained with yohimbine (100 μg/kg) at 1 Hz 20 pulses, 1 Hz stimulation to maximum response, and 5 Hz 50 pulses (Figure 4a). However, yohimbine (1 mg/kg) did not significantly potentiate the cardioaccelerator responses to stimulation (T2-T6) at any frequency, but significantly inhibited responses to short trains of pulses (10 pulses) at 0.5 and 5 Hz (Figure 4b). In controls there was

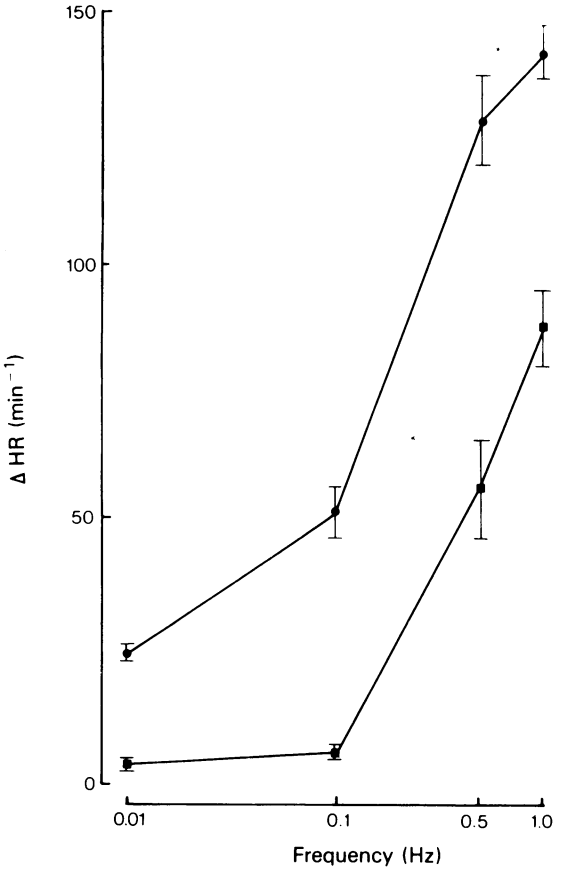

Figure 3 Cardioaccelerator responses to stimulation to maximum response at vertebral levels C6-T1 (●) or T2-T6 (■). Vertical bars represent s.e. mean; $n = 7$.

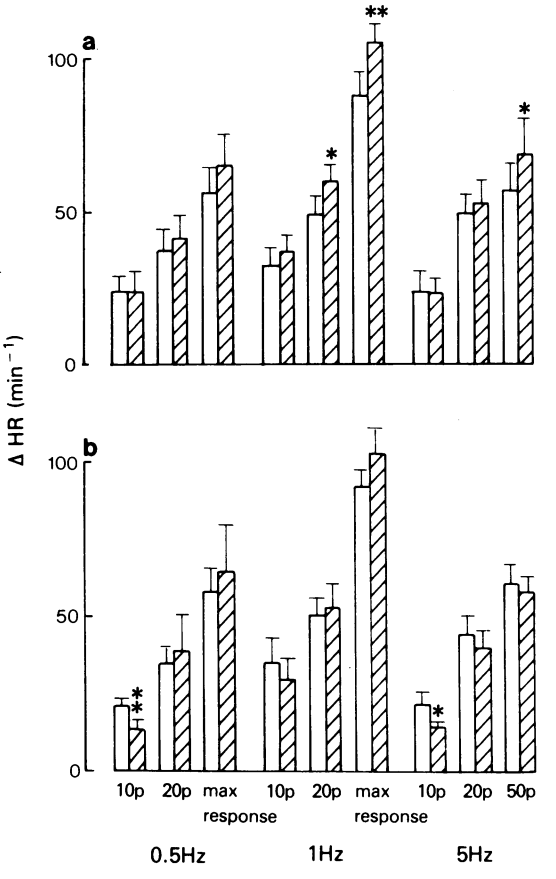

Figure 4 The effects of yohimbine (a) 100 μg/kg or (b) 1 mg/kg on the cardioaccelerator response to stimulation (T2-T6) at frequencies of 0.5 to 5 Hz with trains of 10, 20 or 50 pulses (10p, 20p and 50p respectively), or stimulating to maximum response (max response). Control responses; open columns; responses after yohimbine; hatched. Vertical bars represent s.e. mean. Control responses and responses after yohimbine were compared by Student's t test for paired data; *$0.05 > P > 0.01$, **$0.01 > P > 0.001$. $n = 6$–9.

a small decline of responses following saline (2 ml/kg) but this was not significant.

In adrenalectomized rats ($n = 7$), yohimbine (100 μg/kg) potentiated the cardioacceleration evoked by stimulation at 1 to 5 Hz (T2-T6), with significant potentiation at 1 Hz 20 pulses, 1 Hz maximum response, and 5 Hz 50 pulses i.e. the same conditions as in control rats.

Effects of yohimbine on the cardioacceleration response in the presence of cocaine

Maximal stimuli Yohimbine (100 μg/kg) failed to potentiate significantly the cardioacceleration response to stimulation (C6-T1) with 20 pulses at frequencies from 0.01 to 5 Hz (Figure 5a). However, in the presence of cocaine (3.3 mg/kg) a small but significant potentiation could be shown at 0.1 Hz where the response was submaximal, but not at higher frequencies where the response was near maximal, although potentiation also occurred at 1 Hz (Figure 5b).

The effects of yohimbine (100 μg/kg) on the sustained response to 0.1 Hz continuous stimulation (C6-T1) were then tested. In rats given cocaine (0.5 mg/kg) the response to 0.1 Hz continuous stimulation (C6-T1) was 74.6 ± 7.8 min^{-1} ($n = 5$) as compared to 53.3 ± 7.1 min^{-1} ($n = 7$) in controls. Under these circumstances yohimbine (100 μg/kg), when injected

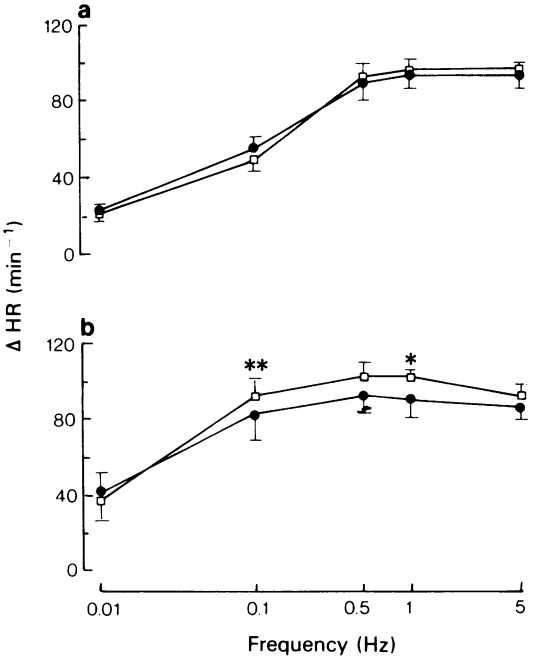

Figure 5 Effects of yohimbine (100 μg/kg) on the cardioacceleration responses to stimulation (C6-T1) with 20 pulses at frequencies from 0.01 to 5 Hz: (a) control, (b) in the presence of cocaine (3.3 mg/kg). Vertical bars represent s.e. mean. Control responses (●) and responses after yohimbine (□) were compared by Student's t test for paired data; *$0.05 > P > 0.01$, **$0.01 > P > 0.001$. $n = 6$–9.

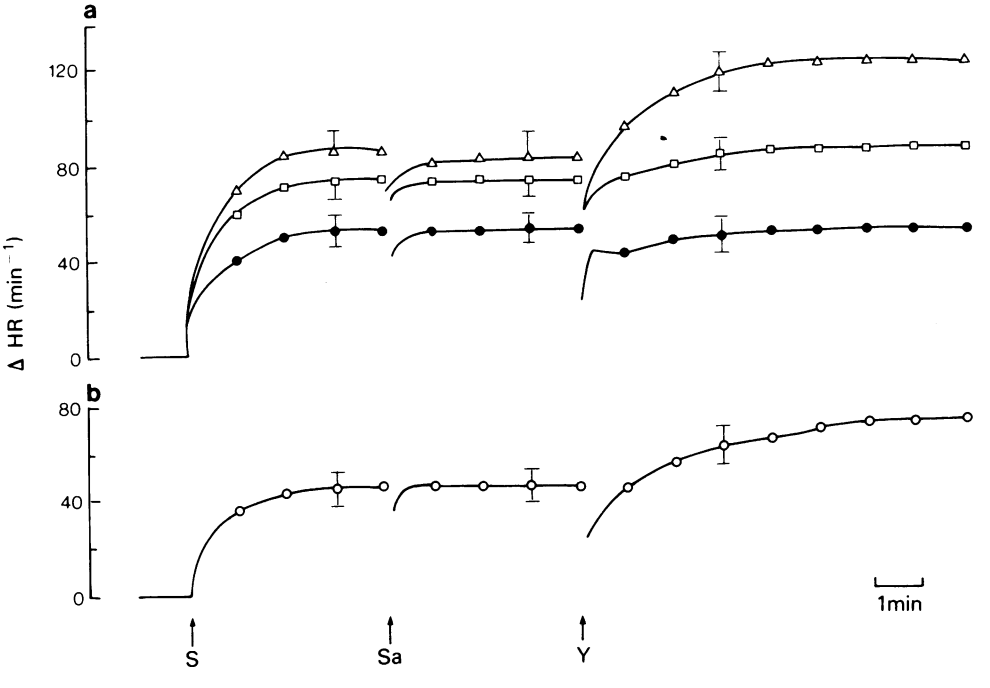

Figure 6 Influence of cocaine on the response to yohimbine (100 μg/kg) injected during the maintained cardioacceleration response to sympathetic stimulation at 0.1 Hz. (a) C6-T1, control responses (●), $n = 7$; responses in the presence of cocaine (0.5 mg/kg) (□), $n = 5$; responses in the presence of cocaine (3.3 mg/kg) (△), $n = 6$. (b) T2-T6, responses in the presence of cocaine (3.3 mg/kg), $n = 5$. Stimulation was started at S, saline was injected at Sa and yohimbine at Y. The graph was constructed as for Figure 1. Vertical bars represent s.e. mean.

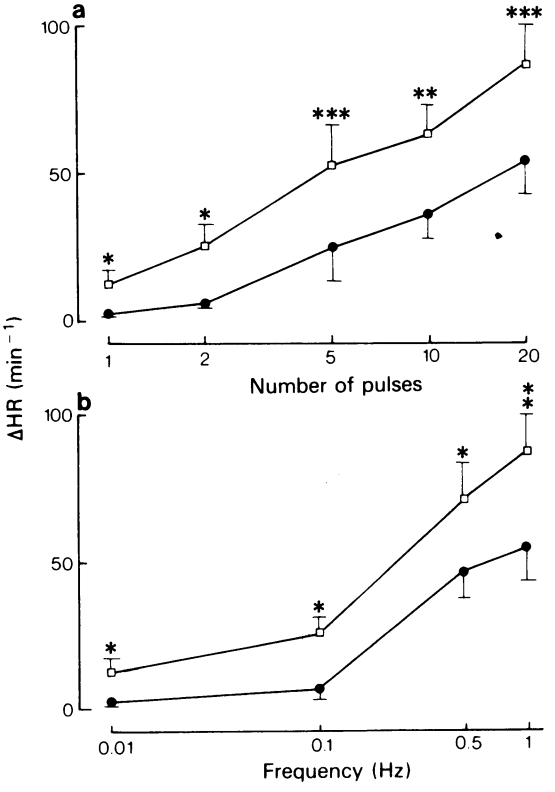

Figure 7 Effects of cocaine (0.5 mg/kg) on the cardioacceleration responses to stimulation at T2-T6. (a) Responses to stimulation at 1 Hz with trains of 1 to 20 pulses; (b) responses to 20 stimulus pulses at frequencies of 0.01 to 1 Hz. Control (●); and after cocaine (□). Vertical bars represent s.e. mean. Control responses and responses after cocaine were compared by Student's t test for paired data; *$0.05 > P > 0.01$; **$0.01 > P > 0.001$; ***$P < 0.001$. $n = 6$.

during continuous stimulation at 0.1 Hz, potentiated the cardioacceleration by 11.5 ± 2.7 min^{-1} ($n = 5$). In the presence of cocaine (3.3 mg/kg) the cardioacceleration response to 0.1 Hz continuous stimulation was 86.2 ± 7.2 min^{-1} ($n = 6$) and yohimbine (100 μg/kg) potentiated the response by 35.3 ± 4.6 min^{-1} ($n = 6$) (Figure 6a).

Submaximal stimuli In the presence of cocaine (3.3 mg/kg), 0.1 Hz continuous stimulation (T2-T6) produced a sustained cardioacceleration of 44.6 ± 6.4 min^{-1} ($n = 5$). Yohimbine (100 μg/kg) potentiated this cardioacceleration by 31.0 ± 9.3 min^{-1} ($n = 5$) (Figure 6b). When expressed as a % of the cardioaccelerator response to 0.1 Hz stimulation, the potentiation due to yohimbine (100 μg/kg) was larger at T2-T6 (76.8 ± 24.8%) than at C6-T1 (37.2 ± 3.8%), in the presence of cocaine (3.3 mg/kg).

Effects of cocaine on cardioacceleration responses at T2-T6

Cocaine (0.5 mg/kg) significantly potentiated the cardioaccelerator responses to stimulation (T2-T6) at 1 Hz with all trains of pulses from 1 to 20 pulses (Figure 7a). Similarly, cocaine (0.5 mg/kg) significantly potentiated the cardioaccelerator responses to stimulation (T2-T6) with 20 pulses at all frequencies from 0.01 to 1 Hz (Figure 7b).

Effects of clonidine and yohimbine on the cardioaccelerator responses to noradrenaline

Both yohimbine (100 μg/kg) and clonidine (100 μg/kg) produced small inhibitions of the tachycardia to noradrenaline (200 ng/kg), with some recovery of the response within 15 min. Yohimbine (1 mg/kg) produced a larger initial inhibition (but not significantly larger

Table 1 Effects of clonidine and yohimbine on the cardioacceleration response to noradrenaline.

		Response to noradrenaline (200 ng/kg)				
		Control response	*Response after test drug*			
Test drug	*Time after test drug (min)*	Δ HR (min^{-1})	Δ HR (min^{-1})	*% of control*	n	P<
Yohimbine	5	42.8 ± 6.8	33.6 ± 7.8	74.8 ± 9.3	5	0.05
(100 μg/kg)	15	42.8 ± 6.8	35.6 ± 6.4	83.1 ± 4.5	5	NS
Yohimbine	5	40.8 ± 5.9	28.5 ± 4.8	69.4 ± 7.4	6	0.05
(1000 μg/kg)	15	40.8 ± 5.9	31.5 ± 3.8	81.3 ± 7.1	6	NS
Clonidine	5	37.1 ± 6.8	28.2 ± 2.3	82.0 ± 13.7	5	NS
(100 μg/kg)	15	37.1 ± 6.8	32.0 ± 4.0	92.0 ± 17.0	5	NS

Values are means ± s.e. means. Control responses and responses after test drug were compared by Student's t test for paired data (NS, not significant, when $P > 0.05$).
Response after test drug was expressed as % of control for each rat.

than that to yohimbine (100 μg/kg)), again with a partial recovery within 15 min (Table 1). However, yohimbine (1 mg/kg) caused a reduction in basal heart rate on injection which recovered to baseline in about 1 to 5 min, whereas clonidine (100 μg/kg) and yohimbine (100 μg/kg) produced only small transient falls in heart rate. The responses to tyramine (5 μg/kg) or isoprenaline (50 ng/kg) were affected in the same way by yohimbine as were the responses to noradrenaline.

Discussion

The results demonstrate that endogenous control of the cardioacceleration response via prejunctional α-adrenoceptors can be uncovered by the use of the selective antagonist, yohimbine. However, this demonstration required careful control of the nature of the stimulation of the sympathetic nerves, due to the maximal or near-maximal response obtained at the frequencies and train lengths required for feed-back inhibition.

The doses of yohimbine necessary to block the prejunctional effect of the exogenous α-adrenoceptor agonist, clonidine, were first established. The nerve stimulus against which clonidine was tested was fixed at 0.1 Hz which gave a submaximal rise in heart rate and, as subsequent experiments showed, no endogenous feed-back which might complicate analysis. The dose of clonidine of 100 μg/kg was chosen as being almost maximal for inhibition of this response (authors' unpublished observations) to provide a rigorous test of the antagonist. Both doses of yohimbine included in the results antagonized the effect of clonidine. The higher dose of yohimbine (1 mg/kg) had a greater antagonist effect but also produced inhibition of the sympathetic response *per se* by an action which was at least partly postjunctional since responses to intravenous noradrenaline were also reduced. Taking this inhibition into account, yohimbine (1 mg/kg) completely abolished the effect of clonidine (cf. Figures 1 and 2). The lower dose of yohimbine (100 μg/kg) was therefore employed as being the largest dose which was sufficiently selective as a prejunctional α-adrenoceptor antagonist. Another antagonist of prejunctional α-adrenoceptors, phentolamine, has been found to depress the beating of guinea-pig atria *in vitro* (Langer, Adler-Graschinsky & Giorgi, 1977).

When given in the absence of any other drug, yohimbine (100 μg/kg) did not significantly modify the response to stimulation at 0.01 to 5 Hz of the spinal outflows at the optimal position of the electrode (C6-T1). This could be interpreted to mean that no feed-back was occurring under these conditions. Alternatively, feed-back may have been present but its partial removal might result in no significant change in the effector response since this was near-maximal in the frequency range 1 to 5 Hz over which endogenous inhibition has previously been demonstrated (Starke, Montel & Wagner, 1971; Langer *et al.*, 1977). However, in certain individual experiments, potentiation did occur, especially when the control response was relatively small. By stimulating the spinal outflow at T2-T6, fewer fibres were activated (although the stimulus pulses were still supramaximal) and hence the response for a given frequency and train length was smaller than that obtained from C6-T1. Under these new conditions, yohimbine could produce small but significant increases in the responses to stimulation at 1 to 5 Hz with trains of 20 or more pulses. No such increases were found with the responses to single pulses, low frequencies or short trains of pulses at high frequencies. The mechanism of the increase appears, therefore, to be quite distinct from that produced by blockade of the neuronal reuptake of noradrenaline by, for example, cocaine. In this latter case, in contrast to yohimbine, the greatest potentiation is of single pulses, and prolongation of the response and potentiation of the response to noradrenaline are characteristically found (Docherty & McGrath, 1977b; 1978).

The requirement for frequencies of 1 to 5 Hz and relatively long trains of pulses also suggests a process which requires a build-up of transmitter in the junction region before it can occur. Presumably, with lower frequencies the transmitter released by each pulse can quickly reach an adequate concentration to trigger the postjunctional effector but the level will have fallen below threshold for the prejunctional effect before the next action potential arrives. Similarly with short trains of pulses at higher frequencies the concentration of transmitter remaining in the junctional gap at the time of arrival of the next pulse may only reach an adequate level for prejunctional inhibition after a number of pulses.

The above interpretation is further supported by the influence of the neuronal reuptake process for noradrenaline on the ability to demonstrate α-adrenoceptor feed-back. In the presence of cocaine the effector responses to sympathetic nerve stimulation were increased in both height and duration (present observations and Docherty & McGrath, 1977b; 1978). This increase in duration cannot be explained solely by an increase in the initial concentration of noradrenaline at the junction. Persistence of an adequate level of noradrenaline in the gap is suggested since the relationship between the height and duration of the response is significantly altered (Docherty & McGrath, 1978). In the presence of cocaine, yohimbine could potentiate responses to maximal or submaximal sympathetic nerve stimulation at the low frequency of 0.1

Hz. This effect of cocaine, like its ability to increase the effector response *per se*, was dose-dependent over the range (0.5 to 3.3 mg/kg) which corresponds with the range over which cocaine produces a dose-dependent blockade of the neuronal accumulation of noradrenaline in the heart of the pithed rat (Muscholl, 1961; Simpson, 1975), and potentiates cardiac sympathetic responses in the pithed rat (Docherty & McGrath, 1977b; 1978). These results, therefore, indicate that in the absence of the major route of transmitter inactivation, the concentration of noradrenaline in the junctional gap is still adequate to stimulate the prejunctional α-adrenoceptors even 10 s after the previous pulse. The importance of the persistence of noradrenaline rather than its initial concentration is emphasized by the effect of yohimbine, in the presence of cocaine, on the response to stimulation (T2-T6) at 0.1 Hz. In this latter case the effector response, although already greatly potentiated by cocaine, is further potentiated by yohimbine whereas the response to stimulation at 0.5 Hz (T2-T6) in the absence of cocaine is not potentiated, even though it is a larger response.

The non-linear nature of the response reduces the usefulness of the heart rate for making quantitative analyses of feed-back mechanisms. However, in our experience, the relative specificity of yohimbine in the heart for the prejunctional α-adrenoceptors compared with postjunctional β-adrenoceptors at least made a semi-quantitative study possible. In other systems tested in the pithed rat where the postjunctional effect was mediated via α-adrenoceptors e.g. vasopressor nerves, yohimbine was not sufficiently selective for the prejunctional α-adrenoceptors and, in doses appropriate for prejunctional blockade, always exerted some postjunctional inhibition (authors' unpublished observations).

The physiological significance of these results is to demonstrate the frequencies and train lengths necessary for α-adrenoceptor-mediated feed-back to occur in the heart. Information is lacking on the frequency of discharge of cardiac sympathetic fibres in conscious animals. However, the available evidence from anaesthetized preparations suggests a phasic discharge of between 1 and 10 Hz with oscillations related to both cardiac and respiratory frequencies (Bronk, Pitts & Larrabec, 1940). Under such circumstances a sufficiently high frequency might not normally be maintained for long enough to produce α-adrenoceptor feed-back at an individual junction. The feed-back might, therefore, operate only in conditions of stress and may act as a safety cut-off rather than as a continuous modulation.

Pharmacological conclusions may also be drawn. First, if the α-adrenoceptor feed-back does not normally operate physiologically, then inhibition of the process with consequent cardiac stimulation might not be expected as a side-effect of α-adrenoceptor blocking drugs except in conditions of stress (see above). Secondly, in assessing the possible effects of agonists at these prejunctional α-adrenoceptors e.g. clonidine, care should be exercised in selection of the test stimulus. At frequencies of $\geqslant 1$ Hz and especially with continuous stimulation or long trains of pulses, endogenous activation of the prejunctional receptors and the near-maximal nature of the effector response might tend to mask any inhibitory effects. Thirdly, the importance of the neuronal re-uptake of noradrenaline in limiting the feed-back at low frequencies might have repercussions for drugs which inhibit uptake and might in consequence activate the α-adrenoceptor feed-back. In turn this would limit the stimulation produced by the uptake blocker but would leave the transmission in a completely different situation with respect to further drugs which affect prejunctional α-adrenoceptors.

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