J. Pharm. Pharmacol. 1979, 31: 767–772 Received February 19, 1978

Effects of pyroxamidine and guanethidine on contractile responses to field stimulation and to noradrenaline in the anococcygeus muscle and vas deferens of the rat

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The effects of pyroxamidine (EMD 21192) and guanethidine on contractile responses were studied in the anococcygeus muscle and vas deferens of the rat. Pyroxamidine (10^{-6} and 10^{-5} M) and guanethidine (6×10^{-6} and 10^{-5} M) potentiated the responses to low concentrations of acetylcholine in the rat anococcygeus muscle. Following incubation of the muscle with 6-hydroxydopamine (10^{-3} M for 3 h), pyroxamidine (10^{-5} M) and guanethidine (10^{-5} M) had no effect on responses to acetylcholine. This suggests that the potentiating effect of pyroxamidine and guanethidine on responses to acetylcholine is due to the release of subthreshold concentrations of noradrenaline.

In the anococcygeus, pyroxamidine (10^{-6} and 10^{-5} M) and guanethidine (10^{-6} and 10^{-5} M) inhibited responses to field stimulation and potentiated responses to exogenously applied (−)-noradrenaline. The responses to field stimulation in the vas deferens were also inhibited by 10^{-5} M pyroxamidine and by 10^{-5} M guanethidine. 10^{-5} M guanethidine, but not 10^{-5} M pyroxamidine, potentiated responses to (−)-noradrenaline in the vas deferens. In the presence of nortriptyline (10^{-6} M), a potent inhibitor of neuronal uptake, the inhibitory effects of pyroxamidine and guanethidine on responses to field stimulation were reduced or reversed and these drugs had no effect on responses to (−)-noradrenaline. This suggests that pyroxamidine is a noradrenergic neuron blocker and that its action is dependent on continued neuronal uptake. Following 6-hydroxydopamine incubation, 10^{-5} M pyroxamidine and 10^{-5} M guanethidine inhibited the responses to (−)-noradrenaline in the rat anococcygeus muscle. Thus it seems likely, at high concentrations, that these compounds have postsynaptic blocking activity.

Pyroxamidine (2-guanyl-1,2,3,10,10a,hexahydro-1,-2,a-pyrazinoindole, EMD 21192) has been shown to have antihypertensive properties following in vivo treatment in rats (Grobecker et al 1977) and in dogs (Schorscher et al 1978). In a comparative study of the catecholamine depleting actions of pyroxamidine and guanethidine in vivo it was shown that pyroxamidine preferentially depletes the adrenaline stores of the adrenal medulla of the rat without having a marked effect on the peripheral noradrenaline stores (Grobecker et al 1977). Guanethidine, by contrast, predominantly depleted noradrenaline stores. Furthermore, on prolonged treatment, guanethidine, but not pyroxamidine, caused degeneration of noradrenergic neurons.

In the present study I have compared the effects of pyroxamidine and guanethidine in vitro. These studies have been performed using the anococcygeus muscle and vas deferens of the rat, both of which receive a dense noradrenergic innervation. Thus I describe the effects of pyroxamidine and guanethidine on contractile responses to field stimulation and exogenously applied (−)-noradrenaline (−)-Na in these tissues.

MATERIALS AND METHODS

Mature male Wistar rats were killed by a blow at the base of the skull and exsanguinated. Anococcygeus muscles were dissected as described by Gillespie (1972). Vas deferentia were removed and dissected free of surrounding tissues. Tissues were mounted longitudinally under 0·5 g tension in organ baths containing a drug-free modified Krebs solution at 37 °C, equilibrated with 5% CO_2 in oxygen. The tissues were allowed to recover for 45 min, the resting tension being maintained throughout. Tissues were placed between 2 platinum electrodes, and were stimulated to contract using biphasic pulses of 1 ms duration and supramaximal voltage. Dose response curves to (−)-NA and acetylcholine (ACh) (anococcygeus only) were obtained non-cumulatively. Stimulation or exposure to agonist was continued for 30 s or, if the response was not fully developed in that time, until the response was fully developed.

The tissues were then allowed to recover, with a minimum period of 5 min, before further stimulation or addition of the agonist occurred. Contractile responses were recorded isometrically using force displacement transducers (Grass model FT03.C) connected to a polygraph (Grass model 79B).

When studying the effect of drugs on contractile responses, the drugs were present in the Krebs solution from the beginning of the recovery period. In the anococcygeus, for the 6-hydroxydopamine (6-OHDA) experiments, each muscle was incubated in the presence of 10^{-3} M 6-OHDA for 3 h and then washed in Krebs solution for 30 min.

The values obtained, under different conditions, were compared using Student's paired *t*-test and were considered to be significantly different when $P < 0.05$. When the maximum responses (g), in the presence and absence of drugs, were not significantly different, responses were expressed as a percentage of the maximum response of the individual dose-response curve (i.e., normalized). For each preparation, a pD_2 value (negative logarithm or molar concentration of agonist producing 50% of the maximum response) was determined by regression line analysis (over the range 20–80% of the maximum response) using a computer. For each pair of tissues, the ability of drugs to potentiate or inhibit responses is expressed as the dose-ratio (the antilog of the difference between the pD_2 values in the presence and absence of drugs). In addition, mean pD_2 values and mean dose-ratios were calculated. When the maximum responses, in the presence and absence of drugs were significantly different, responses were calculated as a percentage of the maximum response of the control dose-response curve.

The drugs used were guanethidine sulphate* (Ciba-Geigy), nortriptyline hydrochloride* (Eli Lilly and Co. Ltd), pyroxamidine hydrochloride* (E. Merck) and acetylcholine chloride, 6-hydroxydopamine hydrochloride and (−)-noradrenaline bitartrate (Sigma Chemicals Ltd). Compounds indicated with an asterisk were generously donated by the companies indicated.

The modified Krebs solution had the following composition (mM): NaCl, 116; KCl, 5·4; $CaCl_2$, 2·5; $MgCl_2$, 1·2; NaH_2PO_4, 1·2; $NaHCO_3$, 22·0; D-glucose, 11·2; Na_2 EDTA, 0·04.

RESULTS

Anococcygeus muscle

In Krebs solution alone. Pyroxamidine (10^{-7}, 10^{-6}, 10^{-5} M) and guanethidine (10^{-6} and 10^{-5} M) had no effect on the resting tone of the muscle. The magnitude of the maximal contractile responses to field stimulation was reduced by pyroxamidine (10^{-7}, 10^{-6}, 10^{-5} M) and by guanethidine (10^{-6} and 10^{-5} M); Table 1. 10^{-7} M pyroxamidine had no effect on submaximal responses to 0·2–15 Hz. At 10^{-6} M, pyroxamidine and guanethidine were equieffective in that they abolished responses at 0·2–2 Hz and greatly reduced those to 5–40 Hz; for results with 10^{-6} M pyroxamidine see Fig. 1A. The responses at 0·2–2 Hz and at 5–30 Hz were abolished and inhibited, respectively, by 10^{-5} M pyroxamidine (Fig. 1B). 10^{-5} M guanethidine abolished all responses to field stimulation.

Table 1. The effect of pyroxamidine and guanethidine on maximal responses to field stimulation in the rat anococcygeus muscle.

	Maximum responses (Mean g ± s.e.m.) Field stimulation
In Krebs solution alone	
(i) control	6·77 ± 0·43 (6)
(ii) 10^{-7} M pyroxamidine	5·24 ± 0·75 (6)*
(i) control	7·10 ± 0·38 (4)
(ii) 10^{-6} M pyroxamidine	3·11 ± 0·68 (4)**
(i) control	5·34 ± 0·43 (3)
(ii) 10^{-5} M pyroxamidine	1·57 ± 0·43 (3)**
(i) control	6·89 ± 0·90 (4)
(ii) 10^{-6} M guanethidine	2·38 ± 0·46 (4)**
(i) control	6·19 ± 1·52 (4)
(ii) 10^{-5} M guanethidine	0 (4)**

* $P < 0.05$; ** $P < 0.01$ paired *t*-test.
(n) = Number of observations.

Pyroxamidine (10^{-7}, 10^{-6}, 10^{-5} M) and guanethidine (10^{-6}, 10^{-5} M) had no effect on the magnitude of the maximum response to (−)-NA in the muscle. The responses to (−)-NA were potentiated × 1·6 ±0·4 (4) [Mean dose-ratio ± s.e.m.; n = 4], ×4·2 ±2·4 (4), and ×3·1 ± 0·7 (4) by 10^{-7}, 10^{-6}, 10^{-5} M pyroxamidine, respectively, and ×2·0 ± 0·2 (4), and ×12·2 ± 4·4 (4) by 10^{-6} and 10^{-5} M guanethidine (see Table 2 for mean pD_2 values).

The magnitude of the maximal responses to ACh was not altered by pyroxamidine (10^{-7}, 10^{-6}, 10^{-5} M) or by guanethidine (10^{-6}, 6×10^{-6}, 10^{-5} M). 10^{-7} M pyroxamidine had no effect on responses to ACh. 10^{-6} M and 10^{-5} M pyroxamidine potentiated responses to $3 \times 10^{-6} - 10^{-4}$ M and $10^{-6} - 10^{-3}$ M ACh, respectively, and had no effect in the presence of higher concentrations of ACh (for results with

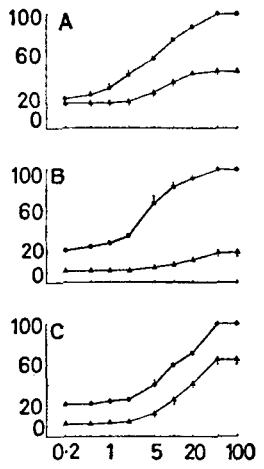

FIG. 1. Effect of pyroxamidine on responses to field stimulation in the rat anococcygeus muscle. Responses to field stimulation in Krebs solution alone (A & B) and in the presence of 10^{-6} M nortriptyline (C); control responses (●—●), in the presence of 10^{-6} M pyroxamidine (■—■), and in the presence of 10^{-5} M pyroxamidine (▲—▲). Responses in (A) and (B) are expressed as a percentage of the maximum response of the individual frequency-response curves and in (C) as a percentage of the maximum response of the control frequency-response curve. Each value is the mean ± s.e.m. from 4 preparations.

Table 2. The effect of pyroxamidine and guanethidine on responses to (—)-noradrenaline in the rat anococcygeus muscle

	(—)-Noradrenaline pD_2 value (Mean ± s.e.m.)
In Krebs solution alone	
(i) control	5·71 ± 0·14 (4)
(ii) 10^{-7} M pyroxamidine	5·89 ± 0·14 (4)*
(i) control	5·63 ± 0·11 (6)
(ii) 10^{-6} M pyroxamidine	6·12 ± 0·17 (6)*
(i) control	5·86 ± 0·13 (4)
(ii) 10^{-5} M pyroxamidine	6·33 ± 0·14 (4)**
(i) control	5·58 ± 0·11 (4)
(ii) 10^{-6} M guanethidine	5·88 ± 0·07 (4)**
(i) control	5·53 ± 0·03 (4)
(ii) 10^{-5} M guanethidine	6·52 ± 0·12 (4)**
Following 6-hydroxydopamine incubation (10^{-3} M for 3 h)	
(i) control	6·80 ± 0·11 (4)
(ii) 10^{-5} M guanethidine	6·51 ± 0·11 (4)*

* $P < 0·05$; ** $P < 0·01$, paired t-test.
(n) = Number of observations.

10^{-5} M pyroxamidine see Fig. 2). Guanethidine, 10^{-6} M, had no effect on ACh responses but at 6×10^{-6} M potentiated the responses to $10^{-6} - 3 \times 10^{-4}$ M ACh while at 10^{-5} M it had no effect on responses to $10^{-6} - 3 \times 10^{-5}$ M ACh although it did potentiate responses to 10^{-4} and 3×10^{-4} M ACh. Thus the maximum response to ACh occurred with a concentration of 10^{-2} M in normal Krebs solution and in the presence of pyroxamidine (10^{-7}, 10^{-6}, 10^{-5} M) or guanethidine (10^{-6}, 6×10^{-6}, 10^{-5} M).

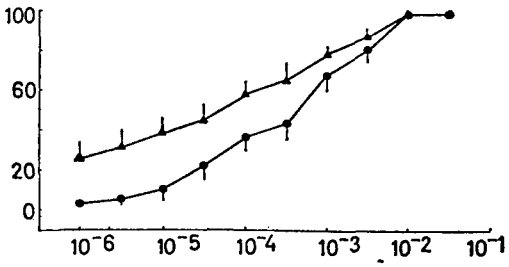

FIG. 2. Effect of pyroxamidine on responses to acetylcholine in the rat anococcygeus muscle. Responses to acetylcholine in Krebs solution alone; control responses (●—●), and in the presence of 10^{-5} M pyroxamidine (▲—▲). Responses are expressed as a percentage of the maximum response of the individual dose-response curve. Each value is the mean ± s.e.m. from 4 preparations.

Following incubation with 6-OHDA

Following incubation of the anococcygeus muscle in the presence of 6-OHDA (10^{-3} M for 3 h), the magnitude of the maximal responses to (−)-NA and ACh were unaltered. Under these conditions pyroxamidine, 10^{-6} M, had no effect on respones to (−)-NA but at 10^{-5} M responses to $10^{-7} - 3 \times 10^{-5}$ M (−)-NA were inhibited (Fig. 3); this inhibition included a decrease in the magnitude of the maximum response from 5·91 g ± 0·50 g [Mean g ± s.e.m.] to 5·09 g ± 0·37 g (n = 4, $P < 0·05$). 10^{-5} M guanethidine had no effect on the magnitude of the maximal responses to (−)-NA, but inhibited sub-maximal responses, ×2·9 ± 0·9 (4) [Mean dose-ratio ± s.e.m.; n = 4]. The responses to ACh, following 6-OHDA incubation, were unaltered by 10^{-5} M pyroxamidine or 10^{-5} M guanethidine.

Vas deferens

In Krebs solution alone, pyroxamidine (10^{-6} and 10^{-5} M) and guanethidine (10^{-5} M) had no effect on the tone of the preparation. The magnitude of the initial and sustained maximal contractile response to field stimulation was unaltered by 10^{-6} M and

reduced by 10^{-5} M pyroxamidine and 10^{-5} M guanethidine (Table 3). 10^{-6} M pyroxamidine had no effect on the initial response to field stimulation at 0·2 and 0·5 Hz, caused a small inhibition of responses at 1–10 Hz, and had no effect at 20–50 Hz. The sustained response to field stimulation was unaffected by 10^{-6} M pyroxamidine. The initial response to 0·5–5-Hz was inhibited by 10^{-5} M pyroxamidine and guanethidine which had a similar inhibitory effect on the sustained responses to 2–50 Hz.

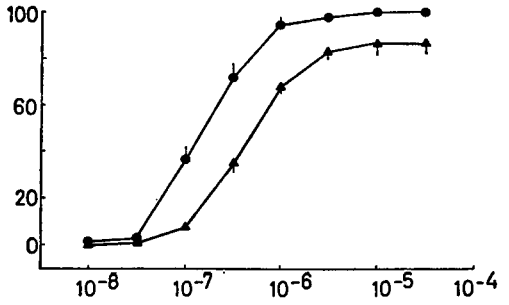

FIG. 3. Following 6-hydroxydopamine incubation, the effect of pyroxamidine on responses to (—)-noradrenaline in the rat anococcygeus muscle. All responses were obtained following 6-hydroxydopamine incubation (10^{-3} M for 3 h); control responses (●—●) and in the presence of 10^{-5} M pyroxamidine (▲—▲). All responses are expressed as a percentage of the maximum response of the control dose-response curve. Each value is the mean ± s.e.m. from 4 preparations.

Pyroxamidine (10^{-6} and 10^{-5} M) had no effect on the responses, including the magnitude of the maximal responses, to (−)-NA, the latter being the unaltered and the submaximal responses potentiated ×1·8 ± 0·3 (4) [Mean dose-ratio ± s.e.m.; n = 4] by 10^{-5} M guanethidine.

In the presence of 10^{-6} M nortriptyline

Nortriptyline (10^{-6} M) had no effect on the magnitude of the maximal responses to (−)-NA, but reduced the maximum responses to field stimulation in the anococcygeus muscle (from 6·54 g ± 0·35 g [Mean ± s.e.m., n = 21] in Krebs solution only to 4·38 ± 0·12 g, n = 12, $P < 0.0005$, unpaired *t*-test) and in the vas deferens of the rat (initial response, from 5·27 g ±0·19 g, n = 12, to 3·21 g ± 0·18 g, n = 8, $P < 0.0005$, unpaired *t*-test: Sustained response, from 4·31 g ± 0·16 g, n = 12, to 1·22 ± 0·15, n = 8, $P < 0.0005$, unpaired *t*-test).

Anococcygeus. In the presence of nortriptyline, 10^{-6} M, pyroxamidine and guanethidine 10^{-6} M had no effect on contractile responses to field stimulation

Table 3. The effect of pyroxamidine and guanethidine on maximal responses to field stimulation in the rat vas deferens

	Maximum response (Mean g ± s.e.m.) Field stimulation	
	Initial	Sustained
In Krebs solution only		
(i) control	5·60 ± 0·08 (4)	4·41 ± 0·39 (4)
(ii) 10^{-5} M pyroxamidine	2·53 ± 0·20 (4)**	1·06 ± 0·20 (4)**
(i) control	5·10 ± 0·29 (4)	4·32 ± 0·28 (4)
(ii) 10^{-5} M guanethidine	0·98 ± 0·22 (4)**	0·36 ± 0·11 (4)**
In the presence of 10^{-6} M nortriptyline		
(i) control	3·49 ± 0·28 (4)	1·35 ± 0·25 (4)
(ii) 10^{-5} M guanethidine	2·31 ± 0·44 (4)*	0·41 ± 0·08 (4)*

* $P < 0.0025$; ** $P < 0.0005$, paired *t*-test. (n) = Number of observations.

in the muscle. The responses at 0·5–5 Hz and 10–30 Hz were inhibited and potentiated, respectively, by 10^{-5} M pyroxamidine (Fig. 1C); this potentiation included an increase in the maximum response from 3·83 g ± 0·50 g to 4·78 g ± 0·31 (n = 4, $P < 0.025$). 10^{-5} M guanethidine inhibited all responses to field stimulation. The responses to (−)-NA, in the presence of 10^{-6} M nortriptyline, were unaffected by pyroxamidine and guanethidine (10^{-6} and 10^{-5} M).

Vas deferens. In the presence of nortriptyline (10^{-6} M), 10^{-5} M pyroxamidine had no effect and 10^{-5} M guanethidine reduced the magnitude of the maximal responses to field stimulation (Table 3). 10^{-5} M pyroxamidine had no effect on the initial responses to 0·2–50 Hz. The sustained response to 2–10 Hz was inhibited by 10^{-5} M pyroxamidine. 10^{-5} M guanethidine inhibited the initial and sustained response to 0·5–50 Hz. Pyroxamidine and guanethidine, 10^{-5} M, in the presence of nortriptyline, 10^{-6} M, had no effect on responses to (−)-NA.

DISCUSSION

The rat anococcygeus muscle has no cholinergic innervation (Gillespie 1972; Burnstock et al 1978). However, the tissue does contract in the presence of ACh; these responses are mediated via muscarinic receptors as they are abolished in the presence of atropine (Gillespie 1972) and unaffected by phentolamine (Doggrell & Paton 1978a). Guanethidine releases NA in the rat anococcygeus muscle (Gillespie 1972; Doggrell & Paton 1978b; Foster et al 1978). In this tissue the contractile responses to ACh are potentiated by guanethidine (Doggrell & Paton 1978a). This potentiation is due to the release of subthreshold concentrations of NA. In the present study, pyroxamidine also potentiated responses to ACh in this tissue. The following evidence suggests that this potentiation is due to the release of NA.

Subsequent to the incubation of the rat anococcygeus muscle with 6-OHDA (10^{-3} M for 3 h), the contractile responses to tyramine are abolished, responses to NA are potentiated and ^{3}H-NA accumulation is reduced (Doggrell & Woodruff 1978). This suggests that the incubation with 6-OHDA depletes the NA stores and also causes a partial destruction of noradrenergic neurons. After such treatment, pyroxamidine had no effect on responses to ACh. Thus it seems likely that in a similar manner to guanethidine, pyroxamidine potentiates responses to ACh by releasing subthreshold concentrations of NA.

It has been suggested that in vivo guanethidine is a more potent releaser of NA than pyroxamidine (Grobecker et al 1977). However, in the present study, at 10^{-5} M, pyroxamidine caused a greater potentiation of responses to ACh than guanethidine. Thus at 10^{-5} M pyroxamidine causes a greater release of NA than guanethidine. The reason for this apparent difference in results may be as follows. The NA releasing ability of guanethidine is more prevalent at lower concentrations. Thus, 6×10^{-6} M guanethidine caused a greater potentiation of contractile responses to ACh than did 10^{-5} M guanethidine.

Guanethidine is a noradrenergic neuron blocker. Thus guanethidine inhibited the contractile responses to field stimulation and potentiated responses to exogenously applied NA in the anococcygeus muscle. Pyroxamidine had similar effects on these responses. This suggests that pyroxamidine is also a noradrenergic neuron blocker. Furthermore, it seems likely that pyroxamidine has a similar potency to guanethidine in this aspect as at 10^{-6} M these compounds were equieffective in inhibiting responses to field stimulation and in potentiating responses to NA in the rat anococcygeus muscle.

In Krebs solution alone at a high concentration (10^{-5} M) guanethidine caused a greater inhibition of responses to field stimulation and a greater potentiation of responses to NA than pyroxamidine in the anococcygeus muscle. However, at this high concentration, noradrenergic neuron blocking is not the only action of these drugs. Thus, firstly, at 10^{-5} M these compounds release NA; pyroxamidine having the greater ability in this aspect. It seems likely that this limits the ability of 10^{-5} M pyroxamidine to inhibit contractile responses to field stimulation. Secondly, at 10^{-5} M, these compounds have blocking activity at the postsynaptic level. Following 6-OHDA dopamine incubation of the muscle (i.e. when the NA stores are depleted and the noradrenergic neurons are partially destroyed), any effect of a drug on responses to exogenously applied NA must occur, predominantly, postsynaptically. Under these conditions, at a concentration of 10^{-5} M, guanethidine and pyroxamidine inhibited the contractile responses to NA. In this aspect, pyroxamidine had the greater effect. This is a possible explanation of the lesser ability of 10^{-5} M pyroxamidine to potentiate responses to NA than 10^{-5} M guanethidine in Krebs solution alone.

Although the vas deferens of many species (e.g. rat, guinea-pig, rabbit) have a dense noradrenergic innervation (Sjöstrand 1965) there is conflicting evidence as to whether NA is the transmitter released by the motor innervation (Ambache & Zar 1971; Furness 1974; Huston et al 1977; Jenkins et al 1975; Simon & Van Maanen 1976; Swedin 1971; Wadsworth 1973). Thus, having established that guanethidine and pyroxamidine are equipotent noradrenergic neuron blockers in the rat anococcygeus muscle, it was of interest to examine the effect of these drugs on the responses to field stimulation in the rat vas deferens. Guanethidine (10^{-5} M) inhibited both the initial and sustained response to field stimulation and potentiated the responses to NA in the tissue. This suggests that the responses to of the tissue field stimulation are mediated by NA.

A higher concentration of pyroxamidine was necessary to inhibit responses to field stimulation in the vas than in the muscle. Furthermore, the responses to NA in the vas were unaltered by pyroxamidine. Thus in this tissue, guanethidine appears to be a more potent noradrenergic neuron blocker than pyroxamidine. However, guanethidine was less potent in this aspect than in the anococcygeus muscle. One possible explanation of this low susceptibility of the vas deferens to noradrenergic neuron blockers is that its structure limits the access of the drugs to the nerve endings. This has been suggested to explain the low susceptibility of the field stimulation responses to certain α-adrenoceptor antagonists in this tissue (Furness 1974; Jones & Spriggs 1975). Furthermore, it is possible that the apparent potency difference between guanethidine and pyroxamidine in the vas deferens but not the anococcygeus muscle results from guanethidine gaining greater access to the nerve endings in vas deferens than does pyroxamidine.

The noradrenergic neuron blockade produced by guanethidine is antagonized by drugs that inhibit the neuronal uptake of noradrenaline (Mitchell & Oates 1970; Maxwell & Eckhardt 1975; Huston et al 1977). Thus the noradrenergic neuron blockade

observed with guanethidine is dependent on continued transport into noradrenergic neurons. Nortriptyline is a potent inhibitor of the neuronal uptake of NA in the rat anococcygeus muscle (Doggrell & Woodruff 1977). In the present study nortriptyline reversed or reduced the ability of pyroxamidine and guanethidine to inhibit responses to field stimulation and to potentiate responses to NA in the anococcygeus muscle and vas deferens of the rat. Thus the noradrenergic neuron blocking action of pyroxamidine is dependent on neuronal uptake in a similar manner as that observed with guanethidine.

Acknowledgements

The author is grateful to Lynn Vincent for her skilled technical assistance. This work was supported by the National Heart Foundation of New Zealand and the Auckland Medical Research Foundation.

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