CHARACTERISATION OF ALPHA-ADRENOCEPTORS OF RAT SUPERIOR MESENTERIC-PORTAL VEIN

MUIR C.K.

SHAHARY ALIAS

SUMMARY

The effect of specific alpha$_1$ or alpha$_2$ adrenoceptor agents on the response of rat superior mesenteric-portal vein to field stimulation was investigated. In a dose related manner, phenylephrine (alpha$_1$ agonist) and yohimbine (alpha$_2$ antagonists) increased while prazosin (alpha$_1$ antagonist) and clonidine (alpha$_2$ agonist) decreased the response of the vein to field stimulation. These effects are the same as those seen with these agents on rat and mouse vas deferens. It is suggested that, as in vas deferens, alpha$_1$ postsynaptic and alpha$_2$ presynaptic receptors exist in rat superior mesenteric-portal vein and that these receptors may be sufficiently sensitive in vein for their existence to be of significance in the action of these agents at clinical doses.

INTRODUCTION

Approximately half the blood volume lies within the venous system and, as such, alteration in venous tone could have major effects on haemodynamics (Sutter, 1965). Activity of veins is presumably controlled predominantly by the adrenergic sympathetic innervation which they receive. The authors know of no evidence to suggest that beta-adrenoceptors are involved in this control, adrenergic contractural effects apparently being mediated by alpha-adrenoceptors only (Muir and Lim, 1980).

Recent theory suggests that alpha-receptors can be sub-classified into two types (Langer, 1974; Langer, 1977). One type, the alpha$_2$ receptor, is situated on the presynaptic nerve ending. Stimulation of this receptor results in membrane stabilization of the presynaptic membrane and, consequently, a reduction in the amount of transmitter released on nerve stimulation. The other type, the alpha$_1$ receptor, is situated postsynaptically on the effector cell membrane. Stimulation of this receptor results in an increased effector cell response to nerve stimulation or, with sufficiently intense stimulation, in the effector cell response itself. The existence of presynaptic alpha$_2$ receptors, stimulation of which reduces transmitter release, has been indicated on a number of different tissues examples of which include rat vas deferens (Doxey *et al.*, 1977; Drew, 1977), mouse vas deferens (Marshal *et al.*, 1978), rat heart (Docherty and McGrath, 1979) and cat spleen (Dubocovich and Langer, 1974).

The subclassification of alpha-adrenoceptors is important because it is relevant to the action of several drugs in clinical use.

The agents used in this study were as follows:

Muir C.K. B.Sc. Ph.D.
School of Pharmaceutical Sciences
Universiti Sains Malaysia,
Penang

Shahary Alias B. Pharm
School of Pharmaceutical Sciences
Universiti Sains Malaysia,
Penang.

$alpha_1$ agonist, phenylephrine (Drew, 1977); $alpha_1$ antagonist, prazosin (Cambridge *et al.*, 1977); $alpha_2$ agonist, clonidine (Doxey *et al.*, 1977); $alpha_2$ antagonist, yohimbine (Starke *et al.*, 1975). The aim of the study was to determine the types of alpha-adrenoceptor involved in the responses to electrically-induced nerve stimulation of rat superior mesenteric-portal vein.

METHOD

Albino rats, weighing 150-200 g, were killed by a blow to the head and bled out. The superior mesenteric-portal vein was removed and split open along its length to allow Ringer solution free access to the outside and lumen side of the tissue during the course of the experiment. This preparation was set up in a 20 ml organ bath containing Tyrode Ringer solution maintained at 32°C and bubbled with compressed air. The composition of the Tyrode was, in mM: NaCl 137, KCl 2.68, $MgCl_2$ 0.87, $CaCl_2$ 1.8, NaH_2PO_4 0.68, $NaHCO_3$ 11.9, glucose 5.56, pH 7.2.

Contractural responses were recorded via a Grass force-displacement transducer (Model FT03C) on a Grass Polygraph (Model 79D). Responses were elicited by field stimulation via silver wire electrodes placed vertically on either side of the tissue. Stimulation characteristics were; every two minutes a 20 second train of pulses, frequency 8 Hz, pulse duration 0.8 msec, maximal voltage. Pulse widths of less than 1.0 msec are capable of eliciting action potentials in nerve membrane but are too short to excite muscle membrane directly.

Using separate tissues, the effect of phenylephrine, prazosin, clonidine or yohimbine on the response to field stimulation was determined by carrying out cumulative dose-response curves for each agent, drug being added one minute before successive trains of electrical pulses.

RESULTS

Phenylephrine (10^{-9} - 2 x 10^{-7}M) caused a dose-related increase in the response to field stimulation, the maximum effect being 124 percent (± s.e. 13.2, n = 4) of control responses (Fig. I). At concentrations greater than 5 x 10^{-8}M) the response to field stimulation appeared to decrease because phenylephrine caused a sustained contracture resulting in a rise in base line.

Prazosin (2 x 10^{-9}-10^{-6}M) caused a dose-related decrease in response to field stimulation (Fig. 2). Yohimbine (2 x 10^{-9}-5 x 10^{-7}) caused a dose-related increase in response to field stimulation, the maximum effect being 112 (± s.e. 4.5, n = 4) of control responses (Fig. 3). Clonidine (2 x 10^{-9}-10^{-6}M) caused a dose-related decrease in response to field stimulation (Fig. 4).

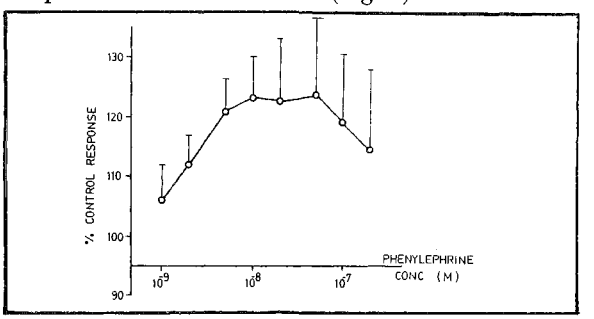

Fig. I Effect of phenylephrine on the response of rat superior-mesenteric portal vein to field stimulation. Vertical bars = s.e., n = 4

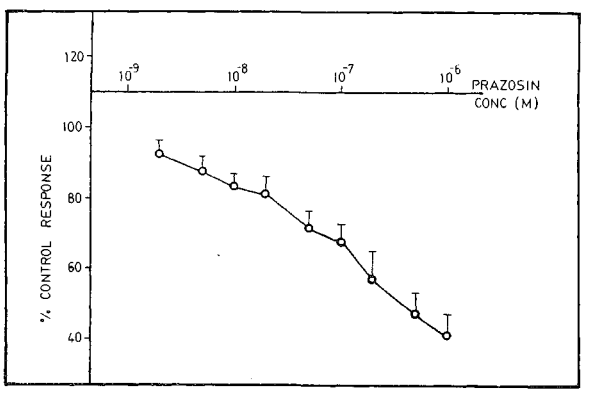

Fig. 2 Effect of prazosin on the response of rat superior-mesenteric portal vein to field stimulation. Vertical bars = s.e., n = 4

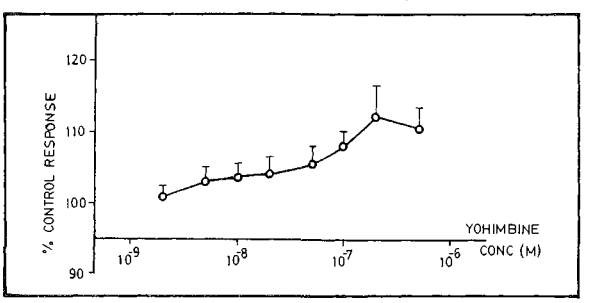

Fig. 3 Effect of yohimbine on the response of rat superior-mensenteric portal vein to field stimulation. Vertical Bars = s.e., n = 4

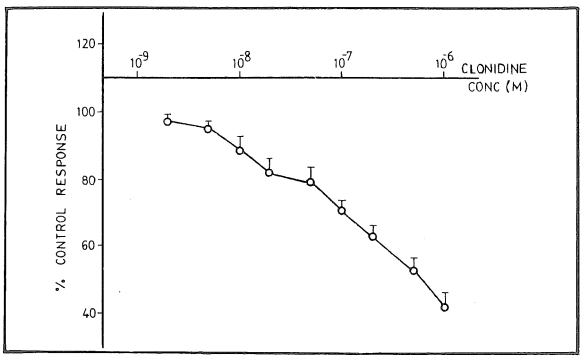

Fig. 4 Effect of clonidine on the response of rat superior-mesenteric portal vein to field stimulation. Vertical bars = s.e., n = 4

DISCUSSION

At all the concentrations tested, phenylephrine (an $alpha_1$ agonist) and yohimbine (an $alpha_2$ antagonist) increased while prazosin (an $alpha_1$ antagonist) and clonidine (an $alpha_2$ agonist) decreased the response of rat superior mesenteric-portal vein to nerve stimulation. These are the same effects seen with these agents on the response to nerve stimulation of rat and of mouse vas deferens (Drew, 1977; Brown, *et al.*, 1979; Marshal *et al.*, 1978). Vas deferens is the tissue upon which much of the research to differentiate types of alpha receptors has been carried out. It therefore seems possible that, as has been suggested for vas deferens, $alpha_1$ and $alpha_2$ receptors are present in vein, that $alpha_1$ receptors are situated postsynaptically on the effector cell membrane and that stimulation of these receptors results in an effector response while $alpha_2$ receptors are situated presynaptically on the nerve ending membrane and that stimulation of these receptors results in a reduction of transmitter release.

It is interesting to note that, in the past, vein has been considered to play relatively little controlling role in haemodynamics. One of the arguments to support this is that veins require relatively large doses of many drugs to elicit responses as compared to arteries. However this experiment indicates that concentrations below 10^{-8}M of the drugs tested have a significant effect on the response to nerve stimulation. This suggests that at therapeutic doses these agents may exert some of their effects by an action on the control of venous tone.

In conclusion, it is suggested that $alpha_1$ postsynaptic and $alpha_2$ presynaptic receptors exist in rat superior mesenteric-portal vein and that they are sufficiently sensitive to drugs for their existence to be of significance in the action of several drugs in common clinical use.

REFERENCES

Brown, C.M., McGrath, J.C. and Summers, R.J. (1979): The effects of alpha-adrenoceptor agonists and antagonists on responses of transmurally stimulated prostatic and epididymal portions of the isolated vas deferens of the rat. *Br.J. Pharmac.* **66** 553-564

Cambridge, D., Davey, M.J. and Massingham, R. (1977): Prazosin, a selective antagonist of post-synaptic alpha-adrenoceptors, *Br.J. Pharmac.* **59** 514 P

Docherty, J.R. and McGrath, J.L. (1979): An analysis of some factors influencing alpha-adrenoceptor feedback at the sympathetic junction in the rat heart, *Br.J. Pharmac* **66** 55-63

Doxey,J., Smith, C.F.C. and Walker,J.M. (1977): Selectivity of blocking agents for pre-and post-synaptic alpha-adrenoceptors *Br.J. Pharmac.* **60** 91-96.

Drew, G.M. (1977): Pharmacological characterisation of the pre-synaptic alpha-adrenoceptors in the rat vas deferens. *Eur.J. Pharmac.* **42** 123-130.

Dubocovich, M.L. and Langer, S.Z. (1974): Negative feedback regulations of noradrenaline release in the perfused cat's spleen: differences in potency of phenoxybenzamine in blocking the pre-and post-synaptic adrenergic receptors. *J. Physiol. (Lond.)* 237 505-519

Langer, S.Z. (1974): Presynaptic regulations of catecholamine release *Biochem, Pharmac.* **23** 1793-1800.

Langer, S.Z. (1977): Presynaptic receptors and their role in the regulation of transmitter release, *Br.J. Pharmac.* **60** 481-497

Marshall, I., Nasmyth, P.A., Nicholl, C.G. and Shepperson, N.B. (1978): Alpha-adrenoceptors in the mouse vas deferens and their effects on its response to electrical stimulation. *Br.J. Pharmac.* **62** 147-151.

Muir, C.K. and Lim Y.M. (1980): Adrenoceptor study of guinea-pig superior mesenteric-portal vein *Med.J. Malaysia* **34** 387-390

Starke, K., Borowski, E. and Endo, T. (1965): Preferential blockade of presynaptic alpha-adrenoceptors by yohimbine. *Eur.J. Pharmac.* 34 385-388.

Sutter, M.C. (1965): The pharmacology of isolated veins *Br.J. Pharmac.* 24 742-751.