Bromocriptine is a potent α-adrenoceptor antagonist in the perfused mesenteric blood vessels of the rat

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Bromocriptine is believed to be a selective dopamine agonist and as such it has been used clinically in the treatment of parkinsonism, acromegaly, and in certain cases of infertility (Greenacre, Teychenne & others, 1976). One of its major side effects is hypotension and this has led to the suggestion that dopaminergic neurons, either central or peripheral, may be involved in the normal regulation of blood pressure (Greenacre & others, 1976; Stumpe, Kolloch & others, 1977). However, it has been demonstrated recently that bromocriptine is a potent α-adrenoceptor antagonist in the rat anococcygeus muscle (Gibson, James & others, 1977). Since a similar action on blood vessels might explain the hypotensive effects of the drug, without dopaminergic involvement, we have investigated the α-adrenoceptor blocking activity of bromocriptine on the pressor responses of the perfused mesentery preparation of the rat.

The mesenteric blood vessels of the rat were dissected and perfused according to MacGregor (1965). Pressor responses to graded doses of noradrenaline and vasopressin were recorded and from these dose-response curves calculated. The antagonist potency of bromocriptine was determined by including various concentrations of the drug in the Krebs perfusion fluid. In other experiments phentolamine was added to the perfusion fluid to observe the effects of an established α-adrenoceptor antagonist on the preparation. The antagonist potencies of phentolamine and bromocriptine were expressed as either the pA_2 or pD'_2 values, which were calculated from the resultant dose-response curves (Van den Brink & Lien, 1977).

The effects of bromocriptine and of phentolamine on the dose-response curves of the perfused mesentery preparation to noradrenaline and vasopressin are shown in Fig. 1. Both drugs reduced the responses of the tissue to noradrenaline. Phentolamine produced a parallel rightward displacement of the dose-response curve to noradrenaline with no reduction in the maximum response. Thus, as expected, phentolamine produced a competitive antagonism with a pA_2 value of $7{\cdot}9 \pm 0{\cdot}1$ ($n = 7$). However, the effect of bromocriptine was different. It reduced both the slope of the dose response curve and the maximum response to noradrenaline, suggesting a non-competitive antagonism ($pD'_2 = 8{\cdot}5 \pm 0{\cdot}2$, $n = 9$). Another difference between phentolamine and bromocriptine concerned the time of onset of block. At least 30 min was required to achieve the maximal blocking effect with bromocriptine, while only 10 min was required with phentolamine.

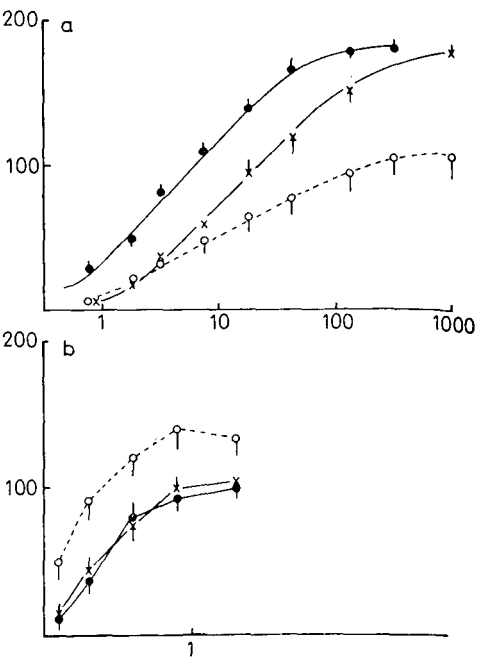

FIG. 1. Dose-response curves of increased perfusion pressure in the perfused mesenteric blood vessels of the rat in response to a: noradrenaline (μg) and b: vasopressin (u). Responses were obtained during perfusion with Krebs solution alone (●——●), Krebs solution + bromocriptine (2×10^{-9} M, ○——○) or Krebs solution + phentolamine (2×10^{-8} M, ×——×). Each point is the mean ± s.e. of at least 6 observations. Ordinate: Increased perfusion pressure (mm Hg).

The drugs also differed in their interaction with vasopressin (Fig. 1). Phentolamine, in a concentration sufficient to produce α-adrenoceptor blockade, did not alter the dose-response curve to vasopressin. Bromocriptine on the other hand caused a marked potentiation of the response to vasopressin.

Previously, bromocriptine has been regarded as a selective dopamine agonist, with only weak effects on α-adrenoceptors (Thorner, 1975; Greenacre & others, 1976). However, the present results indicate that bromocriptine is a powerful, non-competitive α-adrenoceptor antagonist in peripheral blood vessels. Thus it is not surprising that one of the major side effects of the drug is hypotension. While the results do not rule out an involvement of dopaminergic systems in the hypotensive effects of bromocriptine, they do require evidence for such an involvement to be much more substantial. Indeed the potent α-adrenoceptor antagonism produced

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by bromocriptine in smooth muscle (Gibson & others, 1977) and within the cns (Lew, Hata & others, 1977) may explain some of the other diverse actions of this drug.

The effect of bromocriptine on the responses to vasopressin was investigated to check the specificity of any antagonism of noradrenaline. The enhancement of the responses to vasopressin in the presence of bromocriptine is interesting but as yet unexplained. It does not appear to be related to α-blockade since the effect was not observed with phentolamine. At low concentrations bromocriptine exhibited no agonist activity on the preparation, but at high concentrations ($>10^{-4}$ M) a small rise in perfusion pressure was observed. Thus it seems that in addition to α-adrenoceptor blockade bromocriptine exerts a second effect on the blood vessels which potentiates responses to vasopressin.

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Need for Ca ions in the lipolytic action of 5-hydroxytryptamine in rat brown adipose tissue

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Although there are reports of the lipolytic effect of 5-hydroxytryptamine (5-HT) on rat epididymal adipose tissue, the effect has not been resolved. Vaughan (1961) reported 5-HT to stimulate glucose uptake at 0·4 μmol ml^{-1}, but it did not significantly alter free fatty acid (FFA) release by epididymal fat pads. Later, we showed that 5-HT did not alter FFA release by epididymal fat pads but it significantly stimulated release by mesenteric adipose tissue (Itaya & Ui, 1964). Furthermore Bieck, Stack & Westerman (1966) showed the lack of lipolytic activity of 5-HT to be mainly due to its rapid inactivation by monoamine oxidase when incubated with rat epididymal adipose tissue.

In contrast, the lipolytic effect of 5-HT on brown adipose tissue has been described recently (Yoshimura, Hiroshige & Itoh, 1969; Fain, Jacobs & Clement-Cormier, 1973; Steiner, 1973). More recently Steiner & Evans (1976) found that the noradrenaline-like action of 5-HT might be indirect and could be mediated by the release of noradrenaline from neurons within the brown fat-pad. On the other hand, Woolley (1958a) had demonstrated that there was need for Ca ions in the contractions of the rat uterus by 5-HT. Ca ions are required for noradrenaline secretion and hence omission of Ca ions would be expected to result in loss of 5-HT effect if this effect is mediated through the stimulation of noradrenaline secretion.

The present study was designed to examine whether 5-HT promotes lipolysis in the interscapular brown adipose tissue in the absence of Ca ions and the effect of 5-HT was compared with that of noradrenaline in tissue from cold-acclimatized rats.

Interscapular brown adipose tissues were obtained from male Wistar strain rats, 200 to 300 g, maintained on a standard pellet diet (Oriental). Animals were allowed free access to food and water. Some rats were placed into a cold room (4°) for 12 days to test the effect of cold acclimation. After decapitation, tissues were rapidly excised, freed of other white fat and muscle, cut into two or four pieces, and added to the flasks containing 1 ml of Krebs-Ringer bicarbonate buffered solution (pH 7·3) with 20 mg bovine serum albumin (Armour). In experiments testing the requirement for Ca ions, Ca ions were omitted from the incubation medium and EDTA was added to 10^{-3} M. Flasks were gassed with 6% CO_2 in oxygen and incubated for 3 h at 37° in a metabolic shaker. One of each pair of tissues obtained from each rat served as a control. Samples of medium before and after incubation were taken for determination of FFA and glycerol by the colorimetric methods of Itaya & Ui (1965) and Burton (1957) respectively.

Dose response relations are shown in Fig. 1. 5-HT at $2·5 \times 10^{-5}$ M markedly promoted lipolysis of brown