The two alkaloids represent a new nucleus not investigated before for hypoglycaemic effect. Further work on their detailed action on blood sugar, their beneficial effects in diabetes and their structure activity relationships is now in progress.

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October 20, 1964

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Beta sympathetic inhibitory receptors in the small intestine of the guinea-pig

SIR,—The sympathetic inhibitory receptors of the gut of the cat, rat, rabbit, and dog were defined by Ahlquist (1948) as alpha receptors, but it has since been demonstrated that beta receptors also are present in the small intestine of the dog (Ahlquist & Levy, 1959) and rabbit (Furchgott, 1960). Activation of either type of receptor causes an inhibition of the gut.

In the guinea-pig, McDougal & West (1954) showed that the sympathetic inhibitory receptors on the intramural cholinergic neurones have the properties of alpha receptors, and more recently, Harry (1964) in this department has distinguished alpha inhibitory receptors in the circular smooth muscle layer. The results described below (Wilson, 1960) formed part of a communication to the British Pharmacological Society in January, 1960: they give evidence for the presence of beta inhibitory receptors in the longitudinal smooth muscle layer of the guinea-pig gut.

Isolated preparations of guinea-pig proximal small intestine were suspended at 36°, in Krebs solution containing 1 in 10,000 sodium metabisulphite as an antioxidant and bubbled with a mixture of 95% oxygen and 5% carbon dioxide. Longitudinal contractions were produced at 4 min intervals by direct stimulation of the smooth muscle with histamine or methacholine. Graded doses of noradrenaline, adrenaline, isoprenaline or phenylephrine were added to the organ bath 2 min before the next addition of agonist drug and caused an inhibition of the longitudinal contractions. The four sympathomimetic amines produced parallel log dose-inhibitory response curves, but the slope of the curves for the inhibition of histamine was steeper than the slope of the curves for the inhibition of methacholine. Estimates of the pA_2 values of the sympathomimetic amines (Table 1) showed a more pronounced inhibition of histamine than of methacholine, with a ten- to twenty-two-fold difference in potency for the inhibition of the two agonists. The sequence of inhibitory potency of the sympathomimetic amines was isoprenaline the most active, followed by noradrenaline, then

adrenaline and finally phenylephrine which had a very low potency. This order was the same whether the agonist was histamine or methacholine. The potency of isoprenaline was statistically significantly greater than that of noradrenaline

TABLE 1. ESTIMATES OF MEAN pA_2 VALUES ± STANDARD ERRORS FOR THE INHIBITION OF METHACHOLINE AND HISTAMINE CONTRACTIONS, AND APPROXIMATE DOSE EQUIVALENTS RELATIVE TO (±) -ISOPRENALINE

Sympathomimetic amine	Inhibition of methacholine		Inhibition of histamine	
	pA_2 value	Isoprenaline dose equivalents	pA_2 value	Isoprenaline dose equivalents
(±) -Isoprenaline	6·78 ± 0·10	1	7·79 ± 0·08	1
(−) -Noradrenaline	5·94 ± 0·05	7	7·20 ± 0·08	4
(−) -Adrenaline	5·69 ± 0·12	12	6·90 ± 0·17	8
(−) -Phenylephrine	2·75 ± 0·20	10,700	4·09 ± 0·21	5,000

(four and seven times; P = 0·001), adrenaline (eight and twelve times; P = 0·001) or phenylephrine (five thousand and almost eleven thousand times; P = 0·001), but the approximately two-fold greater potency of noradrenaline compared with that of adrenaline was not statistically significant.

Whatever the cause of the observed difference in the inhibition of histamine and methacholine contractions by the sympathomimetic amines, their parallel log dose-inhibitory response curves and their similar relative potencies for the inhibition of either agonist drug are suggestive evidence for an action on a single type of sympathetic receptor. The relative potencies of isoprenaline, noradrenaline, adrenaline and phenylephrine reported above are commensurate with the relative potencies of the same four amines on receptors in the rabbit duodenum which had a high sensitivity to isoprenaline, were blocked by dichloroisoprenaline, but were resistant to blockade by *N*-(2-chloroethyl)-dibenzylamine (dibenamine) or phentolamine (Furchgott, 1960). These receptors were classified as beta receptors. Similarly, in the present experiments with the guinea-pig, the relative inhibitory activities of the four sympathomimetic amines and the high potency of isoprenaline are consistent with an action on receptors of the beta type. The recording of inhibition as a reduction in the contractions caused by direct stimulation of the longitudinal smooth muscle with histamine or methacholine, excludes the inhibitory effects of the sympathomimetic amines on the cholinergic neurones and enables the beta receptors to be sited in the longitudinal smooth muscle.

The results of these experiments together with the findings of McDougal & West (1954) and of Harry (1964), give evidence for the presence of both alpha and beta receptors in the small intestine of the guinea-pig, and moreover, give evidence that the two types of receptor have different locations in the gut.

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October 22, 1964

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