When the permeability-inducing agents were mixed with 0·5 pmol of endothelin, a lower level of Evans blue was extracted compared with saline alone, thus reflecting the intense vasoconstrictor activity.

Subsequently, the effect of endothelin was tested on carrageenan-induced pleurisy, by adding endothelin to the carrageenan. This was without effect possibly because it has recently been found by de Nucci et al (1988, unpublished data) that endothelin is rapidly removed by the lungs.

We have shown that endothelin in low doses is capable of suppressing the increased vascular permeability of rat skin to a variety of agents causing an increase in vascular permeability including EDRF. Both products are derived from endothelial cells and have contrasting actions, endothelin being a potent pressor substance and EDRF having vasodilator activity. We think these two substances could be exerting a local hormonal control or modulation of vascular permeability. These actions may be either part of a normal physiological function or involved in inflammatory reactions. It is known that catecholamines are released at sites of acute inflammation and suppress increased vascular permeability (Willoughby & Spector 1964). It is also recognized that catecholamines induce preproendothelin mRNA, thus leading to the release of endothelin (Yanagisawa et al 1988) which is a potent and longer-lasting vasoconstrictor agent than the catecholamines. This would seem to be a more efficient method of control of the microvasculature than that previously postulated for acting catecholamines.

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References

Furchgott, R. F., Zawadzki, J. V. (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288: 373–376

Griffith, T. M., Edwards, D. H., Lewis, M. J., Henderson, A. H. (1985) Evidence that cyclic guanosine monophosphate (cGMP) mediates endothelium-dependent relaxation. Eur. J. Pharmacol. 112: 195–202

Lykke, A. W. J., Cummings, R. (1969) Inflammation in healing. 1. Time-course and mediation of exudation in wound healing in the rat. Br. J. Exp. Path. 50: 309–318

Palmer, R. M. J., Ferrige, A. G., Moncada, S. (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327: 524–526

Willoughby, D. A., Spector, W. G. (1964) Adrenaline precursors in the inflammatory reaction. J. Path. Bact. 88: 159–166

Yanagisawa, M., Kurihara, H., Kimura, S., Tomobe, Y., Kobayashi, M., Mitsui, Y., Goto, K., Masaki, T. (1988) A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 332: 411–415

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Letter to the Editor

Non-dopaminergic actions of quinpirole hydrochloride (LY 171555), a selective D_2-agonist, in the guinea-pig isolated ileum

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Quinpirole hydrochloride (LY 171555), a selective dopamine (D_2)-receptor agonist, has recently been shown to possess central dopminergic activities in a variety of animal models and is proposed to have potential use in the therapy of Parkinson's disease (Koller et al 1987). Other actions of LY 171555 include an inhibition of intracellular calcium mobilization leading to a reduction in the release of acetylcholine (ACh) from guinea-pig neostriatal slices, mediated through presynaptic D_2-receptors (Fujiwara et al 1987). Such presynaptic depression of transmitter release is also seen with baclofen, a $GABA_B$-receptor agonist (Ong & Kerr 1983), adenosine (Dowdle & Maske 1980) and noradrenaline (Paton & Vizi 1969) in the guinea-pig isolated ileum. We have therefore investigated the interaction of LY 171555 with these presynaptic effects, and now report that LY 171555 antagonized the depression of cholinergic ileal twitch contractions induced by baclofen, adenosine and noradrenaline, an action apparently unrelated to its D_2-agonist properties.

Guinea-pigs of either sex, 200–400 g, were killed by cervical dislocation and bled. Segments of the distal ileum, 3–4 cm in length, were quickly removed and mounted vertically in a 20 mL organ bath containing modified Krebs solution to record

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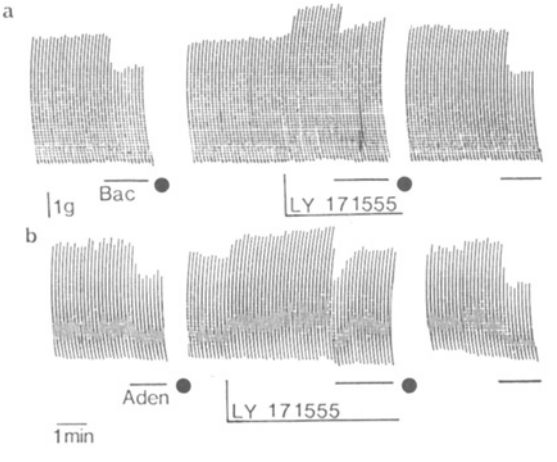

FIG. 1. Depressive responses of repetitive cholinergic twitch contractions in the guinea-pig isolated ileum to exogenously applied a) baclofen (Bac; 10 μM, n = 8) and b) adenosine (Aden; 0·6 μM, n = 8), and antagonism of the depression by baclofen and adenosine with LY 171555 (10 μM). LY 171555 itself induced an enhancement of the twitch contractions. Vertical bar indicates 1 g tension, and the horizontal bar indicates 1 min time interval. ● tissue wash-out.

longitudinal muscle contractions as previously described (Ong & Kerr 1983). Effects of drug treatments were examined on electrically evoked cholinergic twitch contractions of the ileal segments elicited via a pair of ring electrodes connected to a Grass stimulator (0·5 Hz, 0·5 ms duration, submaximal voltage). Mechanical activity of the longitudinal muscle was recorded at a resting tension of 1 g using a Grass Model FT03 force transducer and displayed on a Grass polygraph. All agonists were allowed to remain in contact with the tissue for approximately 2–3 min before tissue wash-out, and antagonists were left in the bath for 3–5 min before further application of agonists. The magnitude of twitch contractions was allowed to recover to control level after each tissue wash-out. The number of experiments performed for each drug was 8, repeated in duplicate on 8 tissues taken from four animals.

Prior application of LY 171555 (10 μM) reversibly antagonized baclofen (10 μM; Fig. 1a)-, adenosine (Sigma, 0·6 μM; Fig. 1b)- and noradrenaline (Sigma, 50 nM; not shown)-induced depression of cholinergic twitch contractions in a dose-dependent, non-competitive manner, giving a non-parallel rightward shift of the dose-response curves for the agonists. This antagonism appeared to be use-dependent, generally reaching a maximum within some 4 twitch contractions following addition of the agonists which themselves first depressed the responses (Fig. 1). The IC50 for LY 171555, a dose which reversed the depressive actions of baclofen (10 μM), adenosine (0·6 μM) and noradrenaline (50 nM) by 50%, was found to be approximately 5 μM for baclofen (n = 8), and 10 μM, respectively, for adenosine (n = 8) and noradrenaline (n = 8). By itself, LY 171555 augmented the height of cholinergic twitch contractions and this effect was not blocked by the D_2-receptor antagonist, sulpiride (5 μM) (Fujiwara et al 1987), which also did not affect individual depressive responses to baclofen (10–50 μM), adenosine (50–100 nM), or noradrenaline (5–50 nM), or the LY 171555 (5–10 μM)-induced antagonism of responses to these agonists. Other D_2-receptor agonists such as RU 24213 (5–10 μM), and D_1-receptor agonists such as SKF 38393 (Research Biochemical Incorporated, 5–10 μM) did not antagonize responses to baclofen, adenosine or noradrenaline, nor did they enhance the twitch height but rather depressed it.

Such use-dependent antagonism induced by LY 171555 on the depressant actions of baclofen, adenosine and noradrenaline, which act through different receptors, suggests that LY 171555 may interfere with the actions of these agonists beyond the receptor level, possibly at the intracellular site whereby they modify calcium influx in response to stimulation. Among the dopamine agonists investigated, only LY 171555 exhibited this antagonist action and showed potentiation of ileal twitch responses at concentrations comparable to those showing D_2-agonist activity in other tissues (Fujiwara et al 1987). Hence, it is unlikely that these actions are related to any D_2-receptor agonist effect of this compound. In comparing pharmacological and therapeutic actions among D_2-receptor agonists, it may be necessary to take into account the present results, in the ileum, which suggest that LY 171555 may not be as specific in its D_2-agonist actions as has been so far thought.

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References

Dowdle, E. B., Maske, R. (1980) The effects of calcium concentration on the inhibition of cholinergic neurotransmission in the myenteric plexus of guinea-pig ileum by adenine nucleotides. Br. J. Pharmacol. 71: 245–252

Fujiwara, H., Kato, N., Shuntoh, H., Tanaka, C. (1987) D_2-dopamine receptor-mediated inhibition of intracellular Ca^{2+} mobilization and release of acetylcholine from guinea-pig restricted slices. Ibid. 91: 287–297

Koller, W., Herbster, G., Anderson, D., Wack, R., Gordon, J. (1987) Quinpirole hydrochloride, a potential anti-parkinsonism drug. Neuropharmacology 26: 1031–1036

Ong, J., Kerr, D. I. B. (1983) $Gaba_A$-$Gaba_B$-receptor-mediated modification of intestinal motility. Eur. J. Pharmacol. 86: 9–17

Paton, W. D. M., Vizi, E. S. (1969) The inhibitory action of noradrenaline and adrenaline on acetychloline ouput by guinea-pig ileum longitudinal muscle strip. Br. J. Pharmacol. 35: 10–28