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The inhibitory effect of paracetamol on the electrically stimulated ileum of the guinea-pig

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Prostaglandin synthetase inhibitors have been reported to inhibit the electrically-evoked contractions of the guinea-pig ileum (Bennett et al 1975). The depressant effect of these drugs is rapidly negated by the addition to the organ bath of prostaglandins E_1 or E_2 (Sokunbi 1979). These findings have led to the suggestion that prostaglandins facilitate cholinergic transmission in this tissue.

In contrast to many peripherally acting analgesics, paracetamol is devoid of anti-inflammatory activity but it has been reported to inhibit prostaglandin synthetase at concentrations ranging from 92 μM–3·9 mM. The ability of paracetamol to inhibit prostaglandin synthetase varies with the tissue being examined; one of the most sensitive is the rabbit brain where paracetamol has an IC50 of 92 μM (Flower & Vane 1974).

We have measured the effect of paracetamol on the guinea-pig electrically-stimulated myenteric plexus-longitudinal muscle preparation (MPLM).

The MPLM was prepared as described by Paton & Zar (1968) and suspended in a 5 cm^3 bath containing Krebs' solution gassed with 95% oxygen and 5% carbon dioxide. Contractions were recorded isotonically under a tension of 0·3 g. Tissues were stimulated through ring electrodes at supramaximal voltage with 1 ms pulses at a frequency of 0·1 Hz. The mouse field stimulated vas deferens preparation was as described by Shaw & Turnbull (1978).

Paracetamol, at concentrations ranging from 10–400 μM produced a dose-dependent inhibition of the electrically evoked contractions of the MPLM (Fig. 1) which was readily removed by washing. However, the inhibitory effect of aspirin, produced over the same range of concentration, persisted even after repeated washing.

In agreement with Sokunbi (1979) that the inhibitory effects of PG synthetase inhibitors are removed by the addition of prostaglandins, we found that paracetamol inhibition was readily negated by PGE_1 2 ng ml^{-1} Fig. 2).

Ehrenpreis et al (1973) have reported that the inhibitory effect of morphine on this tissue is also negated by PGE_1 and PGE_2 at concentrations similar to those we used. We have confirmed the ability of PGE_1 (2 ng ml^{-1}) to negate the inhibitory effect of morphine on the MPLM.

However, the depressant effect of paracetamol and aspirin seen on the MPLM is unlikely to be mediated

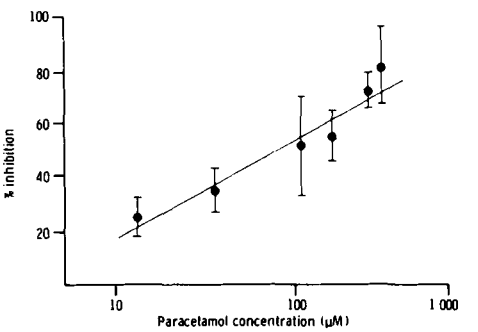

FIG. 1. Dose-response relationship for paracetamol on guinea-pig ileum myenteric plexus-longitudinal muscle preparation. The regression line was calculated from a total of 15 observations.

* Correspondence.

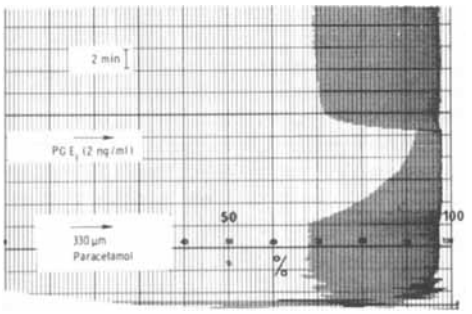

FIG. 2. Guinea-pig ileum myenteric plexus-longitudinal muscle preparation; negation of paracetamol-induced inhibition by PGE_1.

via opiate receptors. We have examined paracetamol and aspirin on other opiate sensitive tissue—the field stimulated mouse vas deferens preparation. At concentrations ranging from 10 μM–1 mM, paracetamol and aspirin were devoid of any inhibitory activity. In contrast, the tissue was sensitive to leu-enkephalin (IC50–15 nM). Furthermore, the inhibitory effect of paracetamol on the MPLM was not negated by the opiate antagonist naloxone at concentrations (10^{-7}–10^{-6} M) which totally antagonized the effect of leu-enkephalin.

Thus we have demonstrated that paracetamol depresses electrically evoked contractions of the MPLM. This effect is negated by PGE_1 which suggests the involvement of prostaglandins in this response.

Paracetamol has an IC50 of 95·2 μM on the MPLM. Flower & Vane (1974) noted that paracetamol inhibited prostaglandin synthesis in the rabbit brain at similar concentrations (IC50 92 μM). Bennett et al (1975) have suggested that prostaglandin synthetase might exist in two pools in the guinea-pig ileum—an extra-neuronal pool, which could be fairly sensitive to low concentrations of indomethacin, and a 'neuronal pool', which is only inhibited by high concentrations of indomethacin. Flower & Vane (1974) found indomethacin to be more potent against synthetase from dog spleen than from rabbit brain, thus demonstrating its low potency in a neuronal system. Conversely, paracetamol was several times more potent in the brain system than in the spleen. This may indicate that paracetamol is relatively specific for the neuronal synthetase system. This would explain why the rabbit brain (IC50 92 μM) and the MPLM (IC50 95·2 μM) are more sensitive to lower concentrations of paracetamol.

Since the concentrations of paracetamol found to be effective in this study are similar to plasma concentration found in man (Prescott et al 1968) it is likely that some inhibition of neuronal PG synthetase occurs during clinical use of this drug.

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[^{3}H]Prazosin and [^{3}H]clonidine binding to α-adrenoceptors in membranes prepared from regions of rat kidney

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[^{3}H]Clonidine is known to bind with high affinity to membranes prepared from guinea-pig renal cortex, while the renal medulla and papilla exhibit much lower levels of specific binding (Summers 1980). Drug displacement studies have shown that the binding site has pharmacological characteristics similar to the α_2-adrenoceptor (Jarrott et al 1979). In contrast, negligible specific binding is observed with [^{3}H]prazosin, a ligand which selectively labels α_1-adrenoceptors (Greengrass & Bremner 1979). In this study, the binding characteristics of [^{3}H]clonidine and [^{3}H]prazosin have been investigated in membranes prepared from rat renal cortex and medulla.

Male Sprague-Dawley rats (150–225 g) were decapitated, and the kidneys rapidly removed and placed on ice. Longitudinal sections were made with a razor blade and the cortex and medulla (including papilla) separated by dissection. Membranes were prepared from these areas as previously described (Summers 1980). One ml aliquots of the final membrane preparation, containing 20 mg ml^{-1} of tissue, were incubated with an equal volume of Tris buffer (50 mM, pH 7·6

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