This could, presumably, explain a slight potentiating effect of THC in combination with CBN found in one study[9].
Our results also show that oral administration of 40 mg of CBD or CBN gives average plasma levels similar to 20 mg THC. Both CBD and CBN levels decrease more rapidly than THC after 6 h. Whether this is due to differences in absorption, distribution or elimination is unclear. The limited pharmacokinetic data available[13], obtained with radiolabeled CBD and CBN, suggest that the latter 2 compounds may have shorter half-lives than THC in man.
The mass fragmentographic assay described here for CBD and CBN is as sensitive as that described for THC, is specific and can be used down to levels of about 0.1 ng/ml for CBN and about 30 pg/ml for CBD.

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Prostaglandin-mediated contractile effect of impromidine and dimaprit in the isolated rat stomach fundus[1]

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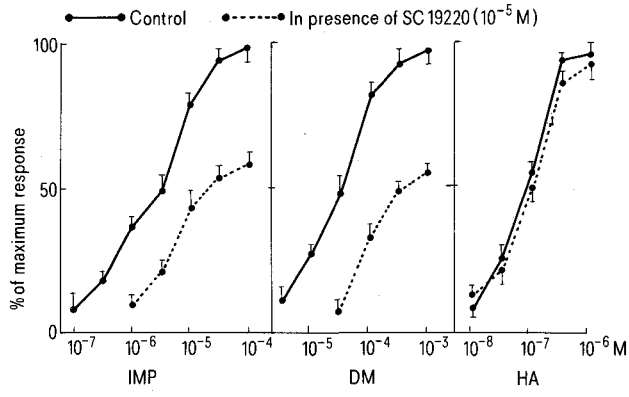
Summary. Impromidine and dimaprit, two newly-synthesized histamine H_2-receptor agonists, have been shown to produce a prostaglandin-mediated contraction in the isolated rat stomach fundus.

The presence of histamine (HA) receptors has been demonstrated in the rat stomach fundus (RSF). The predominant contractile effect of HA on this tissue is mediated through H_1-receptors, while the relaxing effect of the amine is through H_2-receptors[2]. 4-Methyl HA, a pure H_2-receptor agonist, at concentrations of 10^{-8}–10^{-6} M, produces a relaxation in the RSF which can be inhibited by metiamide. However, impromidine (IMP) and dimaprit (DM), all newly-synthetized pure HA H_2-agonists[3,4], have recently been shown to produce a contractile effect in the rat stomach fundus, and this effect could be inhibited by a prostaglandin (PG) receptor blocker and PG-biosynthesis inhibitor. The present study deals with the details of this observation.

Materials and methods. The experiments were performed on isolated RSF strips from adult rats of both sexes, weighing between 200 and 300 g[5]. Strips were continuously superfused with Krebs' solution, aerated with 5% CO_2 in O_2 and maintained at 37 °C, at 10 ml/min flow rate. In some experiments the strips were mounted in an isolated organ bath (10 ml) containing Krebs' solution. Isotonic contractions of the strips were recorded on a kymograph by means of a frontal lever with 12-fold magnification. After an equilibration period of 1 h, the dose-response curves were obtained with IMP, DM and HA before and after SC 19220, a specific PG-receptor blocker[6], was added to the bathing medium. A similar series of experiments was carried out using equipotent concentrations of IMP, DM and HA in the presence of aspirin (ASA), a well-known inhibitor of PG-biosynthesis[7]. Other agonists, 5-HT, angiotensin II and acetylcholine were also tested. The results were expressed as percent of maximum response and statistically evaluated using Student's t-test.

Results. IMP and HA produced a dose-dependent contraction when added to the bathing medium. A similar contraction was obtained with DM at a relatively higher concentration (up to 10^{-4} M). Neither mepyramine (10^{-6} M) nor metiamide (10^{-5} M) altered the responses induced by IMP and DM. Mepyramine, however, at the same concentration competitively inhibited the contractile effect of HA. Atropin (10^{-6} M) and methysergide (10^{-6} M) were also found not to change the contractile response to both H_2-agonists and HA in rat stomach fundus strips. Prior addition of SC 19220 to the bathing medium at a concentration of 10^{-5} M



Dose-response curves of impromidine (IMP), dimaprit (DM) and histamine (HA) before and after SC 19220. A significant inhibition was obtained in the responses to IMP and DM but not to HA. Each point represents the mean value of 10 experiments. Vertical bars show SE of mean.

The effect of aspirin on the contractile effects of histamine, impromidine and dimaprit on the isolated rat stomach fundus strips. The equipotent concentrations of 3 agonists were selected

Agonist	Percent of maximum response		
	Control	In presence of aspirin (10^{-6} M)	Significance
Histamine (10^{-7} M)	53.0±7.0	48.0±6.5	NS
Impromidine (4.2×10^{-6} M)	45.7±4.5	22.0±2.5	$p < 0.001$
Dimaprit (6.8×10^{-5} M)	43.8±6.5	27.0±3.7	$p < 0.05$

Percent of maximum response; mean ± SE of 10 experiments.

significantly reduced the responses to IMP and DM without altering that on HA (fig.). Incubation of the RSF with ASA (10^{-6} M) for a 20-min period caused a significant decrease in the responses to both IMP and DM without altering that of HA when equipotent concentrations of the agonists used were compared (table). The contractile effects of acetylcholine and 5-HT, on the other hand, were not affected by SC 19220 and ASA. However, a similar inhibition was observed in the responses to agiotensin II in the presence of SC 19220 and ASA when tested on the isolated rat stomach fundus.

Discussion. The results of the present investigation indicate that both IMP and DM produce a contractile response in isolated rat stomach fundus strips[8]. This contraction is unlikely to be mediated via H_1 and H_2-receptors since neither mepyramine nor metiamide was able to alter the effects of these compounds. However, the contractile effect of HA was found to be blocked by mepyramine, supporting our previous observation[2]. Furthermore, the contractions induced by IMP and DM were not changed in the presence of methysergide, 5-HT-D receptor blocker, and atropine, a muscarinic receptor antagonist, indicating that these receptors do not play a part in the contractile response to IMP and DM. However, the PG-receptor blocker SC 19220[6] and PG-biosynthesis inhibitor ASA[7] significantly reduced the contractions produced by the 2 compounds as well as by angiotensin II without altering that of HA. The inhibition by SC 19220 and ASA of the contractile effect of angiotensin II has previously been reported[9]. These findings suggest that the contractions in the RSF produced by IMP and DM are PG-mediated. Another HA H_2-receptor agonist, 4-methyl HA, has been shown to produce a relaxation which can be blocked by metiamide[2]. However, no relaxation was obtained in the RSF strips with IMP and DM, an unexpected effect of these compounds which remains to be eluciated.

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Drug uptake by lung slices from paraquat-pretreated rats

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Summary. Lung slices from male Sprague-Dawley rats pretreated with paraquat (PQ) (100 μmoles · kg^{-1}, i.v.) 16 h before sacrifice, accumulated less PQ in vitro than lung slices from saline-treated controls. Neither lung slices from PQ-pretreated nor saline control animals released (effluxed) PQ accumulated in vitro. The accumulation and efflux of imipramine and 5-hydroxytryptamine by lung slices was unaffected by prior in vivo administration of PQ.

The pulmonary absorption of a variety of drugs and chemicals is increased during experimental silicosis[2], papain-induced emphysema[3] and α-napthylthiourea-induced pulmonary oedema[4], possibly due to changes in membrane permeability within the lung. Paraquat is a potent pneumotoxin producing pulmonary oedema, haemorrhage, and ultimately lethal interstitial and interalveolar fibrosis. It might therefore be expected that the paraquat poisoned lung may exhibit altered accumulation and metabolism of various drugs. Indeed in the rat, pulmonary absorption of p-aminohippuric acid and procainamide is increased during paraquat toxicity, reaching a peak 3–5 days after oral administration of the herbicide[5]. However, the changes in pulmonary absorption of organic anions occur in the presence of gross pathological changes in the lung, as judged by increased lung weight and water content. Relatively little is known about pulmonary drug accumulation during the early stages of paraquat-induced toxicity, despite the fact that drug interactions within the lung have been employed in experimental and clinical situations in attempts to ameliorate the course of paraquat toxicity[6–9]. The aim of the investigation described in this communication was to determine the extent to which pulmonary drug accumulation may be altered soon after paraquat administration. Lung slices from control and paraquat-treated rats were used to determine the in vitro pulmonary uptake and efflux of imipramine (IP), paraquat (PQ) and 5-hydroxytryptamine (5HT). These drugs were chosen because the lung accumulates them via different mechanisms[10–14] and hence PQ pneumotoxicity might produce differential effects on the relative rates of uptake and efflux of the compounds.

Materials and methods. Male Sprague Dawley rats (200–250 g) which had been allowed food and water ad libitum were injected i.v. with either saline (5 ml · kg^{-1}) or paraquat (100 μmoles · kg^{-1}) (Sigma Chemical Co.). 16 h later, animals were sacrificed by exsanguination by the severing of the abdominal aorta while under pentobarbital anesthe-