period the next control period was started. The doses were administered in a Latin Square order. The response to a dose of drug was calculated as follows: (Mean amplitude of contraction × frequency in drug contact period) ÷ (Mean amplitude × frequency in control period) × 100%.

The mean response of eleven preparations to 1×10^{-10} g/ml was 100 ± 9 (s.d.)%. 1×10^{-9} g/ml produced a significantly different ($p < 0.05$) response to this of 122 ± 8%. Doses greater than this produced progressively smaller responses, those above 1×10^{-6} g/ml being lower than 100%. The mean response to 5×10^{-3} g/ml was 18 ± 21%.

Cumulative dose response curves to acetylcholine were obtained on tissues maintained at 30°C. Five doses between 5×10^{-8} and 8×10^{-7} g/ml acetylcholine chloride were given at 30 s intervals. Maximal responses to ACh were obtained both at the start and the finish of the experiment.

Responses were expressed as a percentage of a mean of these two. Betamethasone was added to the bath 5 min before the first dose of ACh. Betamethasone in concentrations below 1×10^{-7} g/ml did not affect the response to ACh significantly. Concentrations above 1×10^{-7} g/ml inhibited the response significantly; the dose response curve being shifted downward but not parallely. The response to ACh was completely abolished by 1×10^{-4} g/ml of betamethasone but was recovered after washing.

Cheng & Araki (1978) postulated that anti-inflammatory steroids can inhibit the movement of Ca ions in the muscle of the guinea-pig ileum. Henry, Jackson & Knifton (1973) suggested a similar mechanism in the uterus with betamethasone and cortisol, but also showed that low doses could potentiate the movement of Ca ions. These results suggest that betamethasone may behave in the same way on the rat ileum. However, it would appear that the potentiation of Ca ion movements at low doses is only significant in the spontaneously active and not the ACh-stimulated preparation.

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Chlorimipramine-induced phospholipidosis: biochemical and pharmacokinetic observations

LAURA DELLA CORTE, D. GREMIGNI, IRENE MEGAZZINI, RENATA MOBILIO & G.P. SGARAGLI

Istituto Interfacoltà di Farmacologia e Tossicologia & Istituto di Anatomia Umana Normale, Università di Firenze, Italy

A large variety of amphiphilic cationic drugs which are in widespread clinical use produce a generalized phospholipidosis when administered for prolonged periods in animals. Chlorimipramine (CI) has been reported to induce an accumulation of myeloid bodies, typical of the lipidosis-like drug-induced alterations, in lung and liver cells of chronically treated rats (Lüllmann-Rauch & Scheid, 1975). We have investigated the possibility that these modifications were sustained by an alteration of phospholipid metabolism. Furthermore, as the tricyclic antidepressant drugs are known to accumulate in certain organs, we wanted to verify whether the effects on lipid metabolism could be related to the tissue levels of CI or its demethylated metabolite (DMCI).

Male Sprague-Dawley rats (200–250 g body wt) were treated orally with CI·HCl (Ciba-Geigy, Milano, Italy) in a daily dose of 150 mg (Group A) and 90 mg/kg body wt (Group B) and killed after one week under diethylether anaesthesia. Total phospholipids (TPL) were measured as described by Ruggieri, Fallani & Tombaccini (1976). Tissue levels of CI and DMCI were measured by g.l.c. using a nitrogen detector (Broadhurst, James, Della Corte & Heeley, 1977). The histological examination revealed that CI treatment induced in lung the presence of huge 'foam cells' filled up by myeloid bodies, in a dose related fashion. As shown in Table 1, TPL content measured in Group A animals was markedly enhanced in the lung, while it was slightly modified in the other organs. CI and DMCI tissue levels were measured in Group B animals. The amount of the demethylated metabolite was always higher than that of the parent drug and the DMCI/CI ratio ranged from 16 in the liver to 40 in the lung. As in control animals the TPL content was lower in lung than in liver or kidney, it is suggested that the ability of rat tissues to store DMCI is independent of their basal TPL content.

Table 1 Tissue levels of phospholipids, chlorimipramine (CI) and desmethylchlorimipramine (DMCI) in rats chronically treated with CI

Tissue	*Total Phospholipids** *mg/g of lipid-free dry tissue*	*% of control*	*CI†* *μg/g of wet tissue*	*DMCI†*
Lung	187	246	3.3 ± 0.9	131 ± 27
Liver	130	119	1.5 ± 0.3	25 ± 2
Kidney	128	114	1.7 ± 0.1	41 ± 10
Spleen	82	137	1.4 ± 0.2	47 ± 10
Heart	81	92	0.7 ± 0.1	17 ± 5

* CI was given orally in a daily dose of 150 mg/kg body wt and rats were killed after one week (Group A). Values represent the content measured in the homogenate of pooled organs from 5 rats.
† CI was given orally in a daily dose of 90 mg/kg body wt and rats were killed after one week (Group B). Values are mean ± s.e. mean derived from 5 animals.

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Correlation between the rise in acute phase proteins and histological evidence of ulceration in the rat following indomethacin treatment

M.E.J. BILLINGHAM & MARY J. TUCKER

Departments of Biology and Safety of Medicines, ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire

An increase in the plasma concentration of the acute phase proteins (APP) accompanies the tissue damage associated with most forms of trauma. These APP changes have been used to determine the severity and duration of various inflammatory reactions in animals (Lowe, 1964; Glenn, Bowman & Koslowske, 1968; Billingham & Gordon, 1976) and man (Crockson, Ratcliffe, Payne & Soothill, 1966). The APP have also been used to demonstrate the therapeutic effects of anti-inflammatory and anti-rheumatic drugs (Glenn, *et al.*, 1968; McConkey, Crockson, Crockson & Wilkinson, 1973). Apart from their therapeutic effects however, anti-inflammatory drugs also produce gastro-intestinal irritation and ulceration, especially at high dosage.

We have investigated the changes in plasma concentration of an acute phase protein, α-glycoprotein (α-GP), to establish whether serial measurements of α-GP were a useful, non-invasive means of determining the severity and duration of the gastro-intestinal damage produced by indomethacin.

Male, Wistar derived rats of the Alderley Park strain weighing 170 ± 10 g were used. Indomethacin (Sigma, suspended in 0.5% tween 80) was given as a single oral dose, at various levels, to rats which had been fasted for twelve hours. After treatment, groups of four rats were sacrificed at various times, up to fifteen days. Body weight and α-GP levels were determined at each time and, after sacrifice, one of us (M.J.T.) examined each gastro-intestinal tract macroscopically and microscopically for evidence of ulceration. Blood samples were taken from the caudal vein and α-GP levels determined by radial immunodiffusion (Mancini, Carbonara & Heremans, 1965).

Results are shown in Table 1, which demonstrates the relationship between changes in body weight and α-GP levels, and the histological evidence of ulceration.

The increase in plasma α-GP levels correlated closely with the severity of the gastro-intestinal