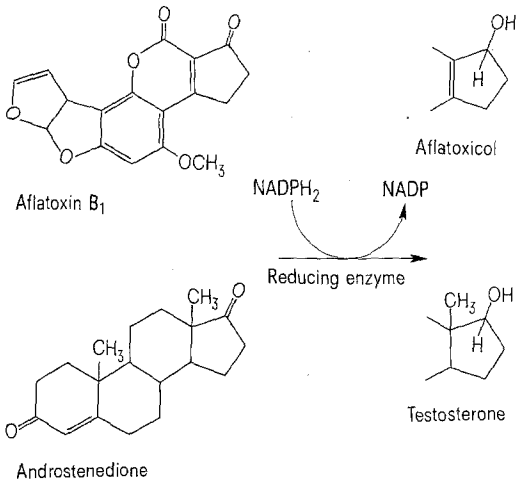

Fig. 1. $NADPH_2$-linked enzymic reduction of aflatoxin B_1 to aflatoxicol and of androstenedione to testosterone. Structural formulae have been drawn to the same scale in order to indicate the broad similarities in substrate configuration.

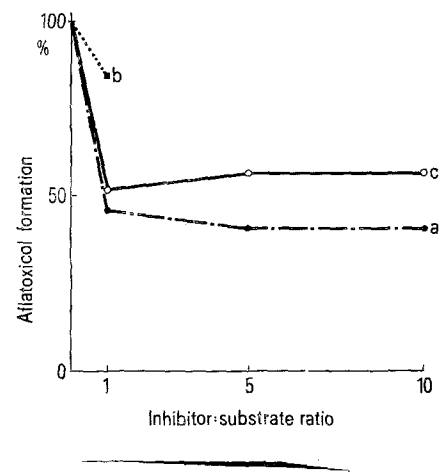

Fig. 2. The inhibition of in vitro aflatoxicol formation by androstenedione (a), and androstenetrione (b), and oestrone (c) in a duck liver homogenate. Substrate concentration: 0.026 mM aflatoxin B_1. 0.05 ml of 105,000 g supernatant liver fraction (10 mg tissue) incubated 15 min at pH 7.4 and 37 °C. Uninhibited rate of aflatoxicol formation: 60 nmoles/g liver/min.

aflatoxin in avian and rabbit livers than in guinea-pig, mouse, and sheep. Each one of the latter species metabolizes the toxin through microsomal pathways (although the major products of metabolism differ[4]) and unlike rabbit and avian livers there is no alternative pathway in the cytosol. Besides having an affinity for microsomal enzymes, aflatoxin appears to compete with steroid sex hormones for binding sites on the endoplasmic reticulum in the rat[2,5] and this may also be true of other species. However, in avian and rabbit livers a soluble enzyme, probably 17-hydroxysteroid dehydrogenase, also competes for aflatoxin. This would tend to modify any toxic effects arising from interaction with the endoplasmic reticulum[6].

Zusammenfassung. Die im Zytoplasma der Vogel- und Kaninchenleber enthaltene NADP-abhängige 17-Hydroxysteroid Dehydrogenase beteiligt sich wahrscheinlich am extramikrosomalen Stoffwechsel des Aflatoxins. Die enzymatische Reduktion des von Aflatoxin B_1 stammenden Cyclopentenons bildet den sekundären Alkohol Aflatoxikol. Diese Reaktion wird durch Androstendion und Oestron gehemmt.

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Effect of Lithium Chloride on the Rat's Paw Edema Induced by Serotonin, Histamine and Formalin

Recently it has been reported from this laboratory that lithium chloride has an analgesic and hypothermic effect in rats when given parenterally[1]. It enhances the analgesic effect of morphine but inhibits its hyperthermic action. This effect has been shown to be somehow related to the effect of lithium ion on brain monoamines, which has been taken into consideration by many authors to explain the ameliorative effect of lithium in the treatment of mania and aggressive behavior [2–5].

Since lithium chloride has an analgesic effect in rats, it appeared of interest to investigate whether this ion also has an anti-inflammatory effect. The present paper describes the results of this investigation.

Methods. Experiments were performed on white male rats from a homogenous strain weighing 150 to 250 g. The animals were fed with a standard rat food and allowed to drink ordinary water *ad libitum*. Experiments were carried out at room temperature (21°C). A group of rats were bilaterally adrenalectomized under ether anesthesia 24 h before the experiments. These animals were given physiological saline solution for drinking. The difference in volume of paw was obtained by measuring the displacement of water level in a specially designed graduated

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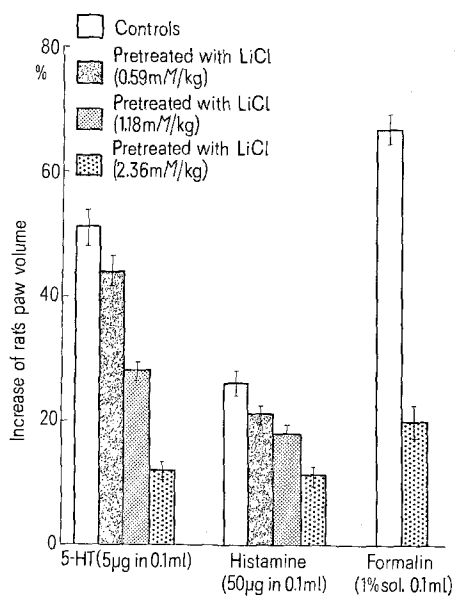
cylinder. Edema was induced by serotonin (5-HT, 0.005%, 0.1 ml = 5 µg), histamine (0.05%, 0.1 ml = 50 µg) and formalin (1%). These agents were diluted in saline and injected into the sole of the right paw; the left paw was used for the control injection of saline. The total volume of injected fluid was 0.1 ml and this amount was kept constant for all experiments. Since the peak swelling time was different for each agonist, the paw volume was therefore determined 45 min after injecting 5-HT, 60 min after injecting histamine and 90 min after injecting formalin. In order to find the interaction between lithium chloride and edema-inducing agents, 2 sets of experiments were designed. In the first experiment lithium chloride alone was administered (5% w/v) i.p. and the paw measured at different intervals, while in the second experiment agonists were injected into the paw at different intervals of time after administration of lithium chloride. It was observed that maximum edema inhibitory effect of lithium chloride was produced when 5-HT or the other agonists were injected 2 h after the administration of lithium chloride. The same procedure was followed with bilaterally adrenalectomized rats and rats pretreated with phenoxybenzamine. Phenoxybenzamine was injected 24 h before the experiment (10 mg/kg i.p.). This drug was preferred as a α-adrenergic blocker because of its long-lasting effect without directly affecting the vessels[6].

The volume change in the experimental paw (right) was compared with that of the control paw (left) and was expressed as a percent increase of paw volume applying the following formula:

$$\frac{\text{right paw volume (ml)} - \text{left paw volume (ml)}}{\text{left paw volume (ml)}} \times 100$$

The results were analyzed statistically using Student's *t*-test.

Results. Intraperitoneal administration of lithium chloride at the dose range of 0.59 to 2.36 m*M*/kg did not change the paw volume of intact, bilaterally adrenalectomized and phenoxybenzamine pretreated rats when compared with saline (0.1 ml/100 g body wt.) pretreated rats. The percentage increase of paw volume following injections of 5-HT, histamine and formalin and the effect of lithium chloride at three different doses in intact rats are summarized in the Figure. Lithium chloride at a dose of 0.59 m*M*/kg decreased significantly the paw edema induced by histamine ($p < 0.05$) but not by 5-HT. However, at the dose of 1.18 m*M*/kg it significantly decreased the swelling induced by both histamine and 5-HT ($p < 0.001$). At a high dose (2.36 m*M*/kg), however, there was significant decrease in paw swelling induced by histamine, 5-HT, and formalin. In bilaterally adrenalectomized rats, 5-HT induced a volume increase of 49.0±3.36%, (S.E.) $n = 8$, which is equal to the volume change of intact rats. Following pretreatment of bilaterally adrenalectomized rats with lithium chloride at the dose level of 1.18 m*M*/kg, injection of 5-HT into the paw induced a volume increase of 46.0±3.16% (S.E.), $n = 8$, which was almost equal to the control values. In phenoxybenzamine pretreated intact rats, 5-HT induced a volume increase of 47.0±3.91% (S.E.), $n = 10$. Lithium chloride given to the phenoxybenzamine pretreated animals at the dose of 2.36 m*M*/kg significantly reduced the 5-HT induced paw edema (7.0± 1.69% (S.E.), $n = 10$).



Effect of lithium chloride on the rat's paw edema induced by 5-HT, histamine and formalin. Each column represents the mean value of 10 experiments. Vertical bars indicate the standard error of the mean.

Discussion. The results indicate that, when given i.p., lithium chloride has an anti-inflammatory effect on the rat's paw swelling induced by 3 different edema-producing agents. Since the lithium ion can reduce the swelling induced by 5-HT, histamine, as well as formalin, it is therefore obvious that it does not act by interferring with the metabolism of exogenously applied 5-HT and histamine. However, recent studies strongly indicate that this ion may play an important role on the uptake, metabolism and release of biogenic amines by neural tissues. This facet may also explain its ameliorative effect on maniac state and aggression[3,4]. The present study clearly shows that bilateral adrenalectomy completely abolishes the anti-inflammatory effect of lithium chloride, thus indicating an indirect mechanism for such an effect. Since phenoxybenzamine pretreatment does not abolish the anti-inflammatory effect of lithium chloride, it is unlikely that the ion causes the release of catecholamines from the adrenal medulla. However, there is, as yet, no evidence concerning catecholamine-releasing action of lithium chloride from the adrenal medulla. It is obvious, therefore, that the anti-inflammatory effect of lithium chloride is probably mediated by the release of corticosteroids from the adrenal cortex. Such an effect of the lithium ion has been previously observed in rats[7] and in patients[8].

Résumé. Administration parentérale de chlorure de lithium inhibe l'œdème de la patte produit par l'injection locale de serotonine, histamine ou formol chez le rat normal mais non pas chez le rat surrénaléctomizé. Ces resultats suggerent que l'effect antiphlogistique du chlorure de lithium est du à une liberation de corticosteroïdes.

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