72.2 mg/g dry weight respectively compared with saline controls (42.8 mg/g) (n=5).

Infusion of oxotremorine (0.34 μg/ml) into the isolated lung for 10 min between the 5th and 6th washes failed to alter the PC content. This was significantly ($2P<0.05$; Mann Whitney U-test) raised from 3.66 (±0.6) to 4.80 (±0.8) mg/g (n=6) by a 10 min infusion of adrenaline (3.4 μg/ml).

The present results suggest that oxotremorine causes secretion of stored lung surfactant by an indirect mechanism involving adrenaline release from the adrenal medulla and subsequent activation of lung β-adrenoceptors.

Reference

ABDELLATIF, M.M. & HOLLINGSWORTH, M. (1977). The *in vitro* and *in vivo* effects of oxotremorine on the phosphatidylcholine content of washes of neonatal rabbit lungs. *Br. J. Pharmac.*, **61**, 502P.

Effects of diazoxide on total lung resistance

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We have shown previously that diazoxide is an effective bronchodilator in guinea pigs (Biggs, Demajo & Peterson, 1977). However, during the course of these experiments we observed an initial dose-related increase in total lung resistance (R_{TL}) in animals given diazoxide. In this paper we report the results of investigations of the initial effects of diazoxide on dynamic lung compliance (C_L) and pulmonary flow resistance (R_L) in anaesthetized guinea pigs, using a method similar to that described by Mead & Whittenberger (1953). In order to eliminate interference from the respiratory muscles, we administered pancuronium bromide (0.1 mg/kg). This drug had no observable effects on C_L or R_L and all of the following experiments were performed in the presence of this drug.

Diazoxide (40 mg/kg), given intravenously, caused a small decrease in C_L and a much more marked increase in R_L. Both parameters usually returned to normal within a period of 4 to 5 min. Bilateral vagotomy or pretreatment of the animals with atropine (0.5 mg/kg) intravenously was without effect on the decrease in C_L and the increase in R_L produced by diazoxide, suggesting that neither vagal reflexes nor a muscarinic action of acetylcholine is involved in the changes induced by diazoxide. In animals pretreated with mepyramine (0.1 mg/kg), intravenously, the increase in R_L produced by diazoxide was abolished but the decrease in C_L was unchanged. In animals pretreated with indomethacin (0.1 mg/kg) or aspirin (1 mg/kg), intravenously, the decrease in C_L was abolished but the increase in R_L was unchanged.

If it is assumed that changes in R_L result mainly from actions on the trachea and large bronchi, whereas C_L is influenced mainly by actions at the level of the respiratory bronchioles and alveoli (Nadel, 1965), then it can be inferred that diazoxide initially increases R_{TL} by two separate mechanisms. Thus the results suggest that diazoxide causes an initial increase in R_L by a direct or indirect histamine-like action on the large airways, an effect that can be blocked by mepyramine. In contrast, the initial decrease in C_L appears to involve the release of prostaglandins or prostaglandin-like substances from the small airways, an action that can be blocked by indomethacin or aspirin.

References

BIGGS, D.F., DEMAJO, W. & PETERSON, M.A. (1977). A comparison of the relaxant effects of diazoxide, aminophylline and isoproterenol, *Proceedings of The Canadian Federation of Biological Societies*, **20**, 124.

MEAD, J. & WHITTENBERGER, J.L. (1953). Physical properties of human lungs measured during spontaneous respiration, *J. Appl. Physiol.*, **5**, 779–796.

NADEL, J.A. (1965). Structure – function relationships in the airways: bronchoconstriction mediated via vagus nerves or bronchial arteries; peripheral lung constriction mediated via pulmonary arteries, *Med. Thorac.*, **22**, 231–242.

A pharmacological study of the mediators released following anaphylaxis of the sensitised hind quarters of the guinea-pig

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Sensitized hind quarters of guinea-pigs were perfused as described for rats and guinea-pigs by Feldberg & Mongar (1954) through the abdominal aorta and the effluent was collected from the vena cava. The effluent from the hind quarters was superfused over the following three bioassay tissues; rat stomach strip (RSS), rat colon (RC) and the longitudinal muscle strip of the

guinea-pig ileum (GI).

Injection of the challenging antigen (BGG, 5 mg/ml per animal) into the Krebs solution perfusing the hind quarters caused a contraction of all three tissues. When mepyramine (0.1 μg/ml) was added to the fluid bathing the tissues, there was no response of the GI, while the RSS and RC still contracted. When samples of perfusate were collected and assayed for histamine fluorimetrically according to the method of Shore, Burkhalter & Cohen (1959) and Evans, Lewis & Thompson (1973), it was found that before challenge the perfusate contained 9 ng/ml, while during the 30 min following challenge it contained 48 ng/ml. It was found that the maximum amount of histamine was released during the first 3–5 min after challenge. The samples were extracted for radioimmunoassay for prostaglandin E_2 and prostaglandin $F_2\alpha$ according to the method of Hennam, Johnson, Newton & Collins (1974) and Jose, Niederhauser, Piper, Robinson & Smith (1976). The mean content of the 30 min perfusate collected before challenge was 0.26 ng/ml prostaglandin E_2 and 0.18 ng/ml prostaglandin $F_2\alpha$, while during the 30 min following challenge the values were 1.34 ng/ml prostaglandin E_2 and 0.41 ng/ml prostaglandin $F_2\alpha$. The difference was only significant in the case of prostaglandin E_2. When indomethacin (1 μg/ml) was added to the fluid perfusing the hind quarters, there was no difference in the prostaglandin content of perfusate collected before and after challenge. The maximum release of prostaglandin was during the period 10–30 min after challenge.

When the challenge was repeated, the contractions of the guinea-pig ileum were considerably greater than after the first challenge. This was not the result of an increase in the amount of histamine release as only 2.7 μg was released after the second challenge compared with 4.2 μg after the first. The increased responses were due to sensitization of the tissue by a material apparently released from the hind quarters as the sensitivity to additions of standard histamine also increased. The increased sensitivity varied from five to one hundred fold, and occurred in 9 out of 15 experiments. The concentrations of prostaglandins released after challenge did not cause sensitization of the GI to histamine.

It is concluded that anaphylaxis in the guinea-pig hind quarters causes the release of histamine followed later by release of a prostaglandin, probably E_2. In addition there was in the majority of experiments, release of an unknown material which sensitized the guinea-pig ileum to histamine.

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References

EVANS, D.P., LEWIS, J.A. & THOMPSON, D.S. (1973). An automated fluorimetric assay for the rapid determination of histamine in biological fluids. *Life Sci.*, **12**, 327–336.

FELDBERG, W. & MONGAR, J.L. (1954). Comparison of histamine release by compound 48/80 and octylamine in perfused tissues. *Br. J. Pharmac.*, **9**, 197–201.

HENNAM, J.F., JOHNSON, D.A., NEWTON, J.R. & COLLINS, W.P. (1974). Radio immunoassay of prostaglandin $F_2\alpha$ in peripheral venous plasma from men and women. *Prostaglandins*, **5**, 531–542.

JOSE, P., NIEDERHAUSER, U., PIPER, P.J., ROBINSON, C. & SMITH, A.P. (1976). Degradation of prostalgandin $F_2\alpha$ in the human pulmonary circulation. *Thorax*, **31**, 713–719.

SHORE, P.A., BURKHALTER, A. & COHEN, V.H. (1959). A method for the fluorometric assay of histamine in tissues. *J. Pharmac. exp. Ther.*, **127**, 182–186.

Evidence from behavioural reactions to fenfluramine, 5-hydroxytryptophan, and 5-methoxy-N,N-dimethyltryptamine for differential effects of short-term and long-term lithium on indoleaminergic mechanisms in rats

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Lithium may impair storage of 5-hydroxytryptamine (5-HT) within nerve terminals, and so interfere with stimulus-release coupling (Collard, 1978), which could explain why its short-term effects on rat behaviour are compatible with reduced physiological availability of 5-HT (Harrison-Read & Steinberg, 1971; Harrison-Read, 1978). After long-term lithium administration (≥2 weeks) however, some of these behavioural effects are no longer apparent, even though indirect measures suggest that the 5-HT storage defect persists (Judd, Parker & Jenner, 1975). Behavioural tolerance may result from 5-HT supersensitivity, which compensates for reduced 5-HT release (Harrison-Read, 1978).

In order to investigate this possibility further, male hooded rats (mean weight 210 g) were pretreated with LiCl 2 mmol/kg i.p. daily for 0 days (saline controls, S), 5 days (short-term lithium, SL), or 21 days (long-term lithium, LL). Nine or 10 rats in each pretreatment group were then given (±)-fenfluramine HCl (10 mg/kg i.p.), (±)-5-hydroxytryptophan (5-HTP, 200 mg/kg i.p., preceded by carbidopa, 25 mg/kg), or 5-methoxy-N,N-dimethyltryptamine (5MeODMT, 1.75 mg/kg i.p.). Fenfluramine releases 5-HT from nerve endings, 5-HTP is the precursor of 5-HT, and 5MeODMT is a putative indoleamine agonist. Rats were examined 8 min after injection of 5MeODMT, and 40 and 120 min after fenfluramine and 5-HTP. Six behavioural features which appear to result specific-