PROSTAGLANDINS E_1 AND E_2 PREVENT BRONCHOCONSTRICTION IN THE GUINEA-PIG

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Prostaglandin E_1 and E_2 aerosols protected the guinea-pig against bronchoconstriction caused by anaphylactic microshock, 1% histamine, 4% acetylcholine and 1% 5-hydroxytryptamine aerosols.

Prostaglandins E_1 and E_2 relax human isolated bronchial muscle (Sweatman & Collier, 1968). *In vivo*, E_1, given as an aerosol to asthmatics, improved the lung function considerably (Cuthbert, 1969; Herxheimer & Roetscher, 1971). In the guinea-pig, Adolphson & Townley (1970) have shown that prostaglandin E_1 antagonizes the bronchoconstrictor effect of methacholine. It therefore seemed of interest, whether, in the guinea-pig, a similar antagonistic effect of prostaglandins exists against the bronchoconstriction caused by anaphylaxis, histamine, 5-hydroxytryptamine and acetylcholine.

Methods The method used for exposing the guinea-pigs to the bronchoconstrictor agent was that of the anaphylactic micro-shock (Herxheimer, 1952; 1955). Female guinea-pigs were exposed in a rectangular plastic box placed on a sponge rubber mat, to the aerosol of a 2% egg albumin solution, 1% histamine acid phosphate, 4% acetylcholine or 1% 5-hydroxytryptamine creatinine phosphate, produced by a nebulizer. The nebulizers used were of the Lewlab type, and the nebulization was effected by a constant air flow of 3 l/min from a compressed air cylinder. Their output in μg/min at this air flow had been determined. The time from the start of the exposure until heavy sneezing or severe dyspnoea of the animal occurred (preconvulsion time) was used as a measure of the bronchial sensitivity to the anaphylactic agent, egg albumin, or to the other bronchoconstrictor substances.

For the experiments with anaphylaxis, the animals, which had been sensitized three weeks beforehand to egg albumin by injection, were exposed at short intervals (1-3 days) so that they became partially desensitized until their preconvulsion time lay between 50-130 s and remained constant at re-exposure after a seven-day interval.

Prostaglandins E_1 and E_2 were kindly supplied by Dr J.E. Pike, Upjohn Co. and by Dr D.R. Maxwell, May & Baker, respectively. Prostaglandin E_1 (120-225 μg) was given as an aerosol from a nebulizer (particle diameter 2-5 μm), prostaglandin E_2 from a pressurized aerosol bottle (particle diameter below 1 μm), in three or four puffs (75-100 μg) through a hole in the animal box which was closed immediately after each puff. When (in a group of 10-12 animals) the preconvulsion time to one of the bronchoconstrictor agents had been established, approximately one week later half of the group was exposed to prostaglandin E_1 or E_2 for 2-5 min and then exposed to a bronchoconstrictor. One week later, the experiment was repeated so that the previously prostaglandin-treated animals were now exposed to the bronchoconstrictor only and the remainder of the group, exposed beforehand, to the prostaglandin. In the anaphylactic microshock experiments this splitting of a group into halves was not possible, because some guinea-pigs become slowly but unevenly desensitized to egg albumin and therefore became useless for further experiments. The half groups thus became too small, making it necessary to leave the groups undivided and to carry out the controls for the whole group one week later. As the experiments proceeded, prostaglandins E_1 and E_2 seemed to have very similar effects, and both substances were then used in alternate experiments.

If an animal did not show any sign of bronchoconstriction or sneezing after 300 s exposure, it was taken out of its box and a preconvulsion time of over 300 s recorded. Presumably, these animals would never have convulsed as they did not show the slightest sign of distress; they appeared completely protected by the prostaglandin. In spite of this presumption, the value of 'over 300 s' was taken to be 300 s for the statistical calculation.

Results There was a uniform and statistically significant protection by both prostaglandins against bronchoconstriction by all four agents used. Naturally, the increase in preconvulsion time (the measure of protection) varied between the constrictor agents, as the amount of bronchoconstrictor was fixed arbitrarily. The means of the preconvulsion times given in Table 1 show the degree of protection; in 25-40% of the prostaglandin-exposed animals the protection seemed complete. The standard error was small; it would

Table 1 Preconvulsion times (PC) of guinea-pigs (in seconds) after exposure to various bronchoconstrictor agents and after similar exposure under protection from prostaglandins (PG).

	PG E_1 and E_2				*Controls*			
	n	*Mean PC*	*s.d.*	*s.e.*	*n*	*Mean PC*	*s.d.*	*s.e.*
Anaphylaxis	33 (10)	217	98	±19	49 (0)	92	39	±5
Histamine	56 (19)	246	73	±10	82 (2)	107	74	±8
Acetylcholine	53 (26)	247	81	±11	90 (2)	69	63	±7
5-hydroxytryptamine	50 (31)	262	70	±10	63 (0)	81	54	±7

The figure in parentheses denotes the number of animals completely protected.

have been smaller still, if the method of producing an aerosol by nebulizer could be made more reliable. In practice, the nebulizer syphon may become partly blocked without being immediately noticeable, or the air pressure from the cylinder may wane prematurely. Both faults would result in the preconvulsion time becoming longer. Another source of variation is an apparently random change of sensitivity in an animal to the agent in question from one day to another. The reason for these, fortunately rare, changes are not known.

Discussion The guinea-pig bronchial tree is a useful experimental tool, which, in its sensitivity to constrictor agents, is very similar to the bronchi of asthmatics or bronchitics. The reaction of the animals to these agents, in some respects, very much resembles human asthma ('guinea-pig asthma'): when the animals become breathless, they put their weight on their forefeet in order to increase their thoracic volume (just as a patient in an attack would lean forward on arms and hands) and gasp for air, the nose reacting by sneezing. The present results show that very small amounts of both prostaglandins E_1 and E_2 protect against bronchoconstriction caused by at least four different substances. This effect has, so far, been shown in naturally occurring asthmatic bronchial spasm (Cuthbert, 1969; Herxheimer & Roetscher, 1971) and, quite recently, in normal subjects (Mathé, Hedquist, Holmgren & Svanborg, 1973). The effect is similar to that of sympathomimetic substances, such as isoprenaline or salbutamol, which also counteract bronchial constriction whatever its cause. However, in contrast to these bronchodilators, the dilator action of the prostaglandin E's is often preceded, in asthmatics, by a strong cough irritation accompanied by bronchial constriction. This bronchial constriction has also been observed by Mathé *et al.* (1973) in about half of their six normal subjects, but, apparently, they have not noticed cough or irritation. In my experiments with Roetscher (1951) it was found that this cough irritation could not be prevented by prior isoprenaline inhalation. That Mathé *et al.* have not observed cough may be due to the fact that we have used greater amounts of prostaglandin E_2 in our experiments.

In view of the strong protection afforded by prostaglandins E_1 and E_2 in these experiments, it appears possible that the amount used was more than required for this effect. It was not possible to carry out experiments in order to determine the minimum amount of prostaglandin needed.

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