Ergotamine (650 ng/ml) infused through rat lungs completely prevented the release of spasmogens and the rise in perfusion pressure induced by tryptamine (2 μg/ml), but had little effect on release induced in the same preparation by histamine (2 μg/ml). This action of ergotamine is comparable to that of methysergide and may be similarly related to blockade of tryptamine receptors in smooth muscle. In contrast, diethylcarbamazine (1 mg/ml) and indomethacin (10 μg/ml) are non-specific antagonists, preventing both tryptamine and histamine induced release. Whereas the antagonism by indomethacin persists for at least 1 h after the end of the infusion, that by diethylcarbamazine ceases within 10 min of stopping the infusion.

Tyramine (10–100 μg/ml) does not induce release of spasmogens from the isolated lungs of rat, rabbit or guinea-pig, although in rat and rabbit lungs it increases perfusion pressure. In cat and dog lungs, tyramine (100 μg/ml) induces both release and a rise in pressure. Dopamine (100 μg/ml) induces release in dog but not in rat, guinea-pig or cat lungs.

Tyramine-induced release in cats' lungs is not prevented by mepyramine (100 ng/ml), methysergide (100 ng/ml), propranolol (2 μg/ml), hyoscine (100 ng/ml), phenoxybenzamine (100 ng/ml), ergotamine (6·5 μg/ml) or haloperidol (200 ng/ml). However, it (and histamine induced release) is non-specifically antagonized by diethylcarbamazine and indomethacin, though perfusion pressure still rises.

We conclude from these results that: (1) the ability of agonist amines to induce release of spasmogens from the lung varies markedly between species; (2) the release may be blocked at two distinct points, one at the level of a specific agonist receptor, and the other at a less specific level perhaps subsequent to activation of smooth muscle receptors.

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Anaphylatoxin-induced release of a substance with prostaglandin-like activity in isolated perfused guinea-pig lungs

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A substantial proportion of the mepyramine-resistant bronchoconstrictor and pressor effects of anaphylatoxin (AT) is subject to tachyphylaxis (Sackeyfio, 1971). This suggests a probable involvement of mediators hitherto not implicated in AT activity. This possibility was investigated using the isolated, perfused guinea-pig lung preparation.

Male guinea-pigs (400–600 g) were used. The lungs were isolated and perfused at a constant rate (5–8 ml/min) with Krebs solution at 37° C through the pulmonary artery (Piper & Vane, 1969). AT (0·01–0·05 ml), prepared by incubating fresh rat serum with inulin (Hicks & Sackeyfio, 1972), was injected into the pulmonary artery and the effluent from the lungs was examined for myogenic activity by the continuous bioassay technique (Vane, 1964; Piper & Vane, 1969). In each experiment two assay tissues, referred to respectively as top and bottom tissues, were arranged in series and superfused with the perfusate from the lungs. A mixture of antagonists, methysergide bimaleate (2×10^{-7} g/ml) and hyoscine hydrobromide (10^{-7} g/ml), was superfused over both tissues in all experiments, to eliminate the possible effects of 5-hydroxytryptamine and acetylcholine respectively. Responses of the tissues were monitored by Ether Strain Gauge transducers (Type TS1) and recorded on a Devices MS-recorder.

Perfusate from AT-shocked lungs caused contraction of segments of guinea-pig ileum. When mepyramine (10^{-7} g/ml) was superfused over the bottom tissue, responses to histamine (2–20 ng) were abolished but the effects of the perfusate were only partially antagonized. Furthermore, repeated injection of AT (0·05 ml) directly over the tissues elicited responses which were subject to tachyphylaxis in both tissues. However, when the assay tissues had thus been made almost completely refractory to directly applied AT, they still exhibited undiminished responsiveness to the effluent from AT-shocked lungs. This indicated that the mepyramine-resistant AT-induced myogenic activity in the perfusate was of pulmonary origin.

In the presence of the mixed antagonists, cat terminal ileum (CTI), rat stomach strip (RSS), rat colon (RC) and chick rectum (CR) were all contracted by the perfusate from the AT-shocked lungs. Cat jejunum (CJ) was not, however, affected. Bradykinin (5–200 ng) contracted both CJ and CTI; histamine (2–20 ng) contracted CTI but not CJ or RSS; prostaglandin E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) (5–25 ng) contracted RSS, RC and CR but not CTI; and adrenaline and noradrenaline (5 ng) caused both CR and RSS to relax.

It can be concluded therefore that the myogenic substances in the AT-shocked lung perfusate were unlikely to be acetylcholine, 5-hydroxytryptamine, bradykinin or catecholamines but had prostaglandin-like as well as histamine-like activity.

These results are consistent with the suggested involvement of myogenic substances hitherto not implicated in AT activity. Further experiments are necessary to distinguish this activity from the possible involvement of slow reacting substance (SRS-A) or rabbit aorta contracting substance (RCS).

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