a potent dopamine antagonist on the dopamine-sensitive adenylate cyclase (Usuda et al 1979). YM-08050 has potent behavioural actions following peripheral administration (Usuda et al 1979), indicating that this compound does penetrate readily into the brain. Thus again there is a link between membrane penetration and blocking activity on the adenylate cyclase.

If our hypothesis is correct it might help clarify what, to us, is one of the anomalies of the D1 and D2 receptor hypothesis. That is that, apart from its lack of effect on the adenylate cyclase, sulpiride has a very similar spectrum of activity to that of the classical neuroleptics. Thus sulpiride, like classical neuroleptics, is a potent stimulant of prolactin secretion (Iwasaki et al 1976), is a potent antiemetic (Laville & Magarit, 1968) and is a potent antagonist of electrophysiological responses to dopamine (Woodruff & Andrews 1979; Pinnock et al 1979). Sulpiride, like other neuroleptics, is also very potent, when applied directly into the rat nucleus accumbens, in blocking the locomotor stimulation produced by dopamine receptor agonists (Woodruff & Andrews 1979).

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Some observations on the pharmacological activity of MIF (Pro-Leu-Gly-NH_2)

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We wish to report some observations on the pharmacological activity of MIF (Pro-Leu-Gly-NH_2) with particular reference to the recent communication of Bjorkman et al (1980) in which they reported the lack of activity of MIF against oxotremorine, fluphenazine and amphetamine-induced behaviour in rats and mice. In common with other workers, including Bjorkman et al, we have failed to confirm the original observations of Plotnikoff & Kastin (1974) that MIF would antagonize the effects of oxotremorine. Nor have we found any antagonism of tremor induced by harmaline (10 mg kg^{-1} i.p.). However, in contrast to Bjorkman et al, we have been able to confirm the observations of Voith (1977) that MIF will antagonize neuroleptic-induced catalepsy in mice. The timing of the MIF injections appear to be critical in this experimental situation.

A just supramaximal dose of haloperidol (10 mg kg^{-1} i.p.) was injected into groups of mice and the presence or absence of catalepsy was assessed 30 min later by placing the mice on a string-wrapped rod (see Zetler 1968; Doggett 1973). When animals were also given MIF (100 mg kg^{-1} s.c.) 10 min before, together with, or 10 min after the haloperidol, there was a 60–80% reduction in the number of animals exhibiting catalepsy in comparison with 0·9% NaCl-treated controls. If the MIF was injected outside this narrow time limit, then no antagonism of haloperidol was seen. 50 mg kg^{-1} s.c. MIF was not effective under similar conditions.

In conclusion, the failure of Bjorkman and his colleagues to find any antagonism of fluphenazine-induced catalepsy may be related to the time-effect course of MIF.

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Complement anaphylatoxin C5a stimulates release of SRS-A-like activity from guinea-pig lung fragments

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A belief that anaphylatoxins are major agents in hypersensitivity reactions is as old as that relating to histamine. Studies on complement during the past eight years have elucidated the biochemistry and functional dynamics of the anaphylatoxin molecules, C3a and C5a. Previous studies concerning the pharmacological responses of tissues to anaphylatoxins usually employed impure material in tests which were heavily biased towards showing the effects of histamine. Thus anaphylatoxins have come to be regarded as releasers to tissue histamine which in turn was believed to cause the various observed responses. Evidence for the ability of anaphylatoxins to release histamine is compelling and has diverted attention from their possible role in mediating other indirect effects or of eliciting direct responses of susceptible cells. We recently reported (Stimler et al 1980) that peripheral strips of guinea pig lung underwent a very strong contraction in the presence of C5a at 1 μg ml^{-1}, a response that was not blocked by high concentrations of histamine antagonists. We have since found that when guinea-pig lung is perfused free of blood, chopped into fragments about 0·2 mm thick and incubated for 10 minutes in Tyrode solution at 37 °C, the addition of 1 μg ml^{-1} of purified C5a induces the release of little histamine (15–20% of total; although significant amounts of a substance which appears to be a leukotriene are found. Furthermore, we find that contraction of the guinea-pig gut, previously rendered tachyphylactic to C5a, has a profile characteristic of SRS-A, and is blocked by FPL 55712, an inhibitor of SRS-A (Augstein et al 1973).

The quantities of SRS-A-like activity present in the lung supernatant are not large (120–130 U g^{-1} lung), but it is likely that much of the activity is taken up by the tissue after being synthesized. We do not yet have either authentic standards or specific assays for leukotrienes (eg R.I.A.) so that identity of the active substance remains somewhat tentative. Furthermore, the release of mediators in addition to histamine does not exclude the possibility that C5a also acts directly on the tissues.

Our findings indicate a much wider role for complement in lung pathophysiology than has previously been envisaged. C5a will be generated via both the classical (antibody) and alternative (tissue enzyme) routes of complement activation and will therefore be present in conditions such as farmer's lung and bronchitis.

The present work suggests that the final mediator substances histamine and SRS-A, which are known to produce bronchoconstriction in asthma, may also contribute to the dyspnoea in lung diseases which involve activation of complement.

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