Anti-inflammatory action of corticosteroids

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Summary

The anti-inflammatory action of corticosteroids is complex. At a cellular level, they cause redistribution of granulocytes, resulting in increased circulating granulocytes and reduced tissue pools. They also cause lymphopenia. The significance of these phenomena in relation to the anti-inflammatory activity of steroids is unknown. The most obvious pharmacological effects of corticosteroids are seen on blood vessels. They cause adrenergically mediated vasoconstriction and non-competitive antagonism of vasodilation due to prostaglandin E and bradykinin.

Prostaglandin formation is inhibited by corticosteroids but whether this is due to an effect on enzymic synthesis or release is uncertain. Corticosteroids stabilize the lysosomal membrane preventing release of lysosomal enzymes *in vitro* but the significance of this *in vivo* is debatable.

THE corticosteroids differ from almost all other anti-inflammatory drugs in that they are capable of inhibiting virtually all the components of inflammation. It is proposed to deal with the anti-inflammatory action of corticosteroids on three interrelated components of the inflammatory response: (i) inflammatory cells; (ii) blood vessels; (iii) release or formation of mediators.

Before embarking on this scheme it is worth considering some general features common to most inflammatory responses. Figure 1 shows an inflammatory response in its simplest form. The response to injury is bimodal. There is an initial transitory increase in vasoactivity which soon dwindles. It is soon followed by a gradual rise to a sustained plateau of vasodilatation or increased permeability. The delayed phase of the reaction finally dwindles after about 24 hr or more. The biphasic reaction can be identified clinically although it is often overlooked. In the skin an immediate transitory erythematous phase occurs after short wavelength u.v. irradiation, to be followed by the characteristic delayed 'sunburn' erythema.

Much effort has gone into the identification of mediators which bring about this dual response. However, the natural history of most inflammatory

FIG. 1. Simple representation of inflammatory response. A = mast cell, B = polymorphonuclear, C = monocyte.

responses to injury leads to spontaneous remission. It may well be that the pharmacological and cellular mechanisms involved in the natural termination of inflammation are just as important in terms of understanding the pathology and therapy of inflammation as the mechanisms involved in its production.

The initial phase of the inflammatory response is due to released histamine from the tissue mast cell. Experiments with cytotoxic polymorphonuclear depleting agents (Willoughby and Spector, 1968) suggest that polymorphs, if involved, may play only a minor part in the delayed response because granulopenic animals show a normal delayed response. On the other hand, the appearance of mediators of the delayed response appears to be associated with mononuclear leucocytes.

The interactions of the mediators of the delayed reaction are probably very complex. The E prostaglandins (PGE) and the F prostaglandins (PGF), both of which are present in the delayed inflammatory response, act in opposition to each other, PGE causing vasodilatation and PGF causing vasoconstriction (Crunkhorn and Willis, 1971). The spontaneous resolution of inflammation could well be a result of an increase in the proportion of F

relative to E. At the same time PGE enhances the inflammation—producing potentiation of pharmacological actions of histamine and bradykinin (Moncada, Ferreira and Vane, 1973). Thus PGE, in doses which alone do not cause whealing, will amplify whealing due to histamine or bradykinin. Synergism seems to be an important factor in the pharmacology of delayed inflammation. PGE has a further action on secretion of histamine. PGE causes inhibition of histamine secretion by mast cells via a negative feedback mechanism (Lichtenstein *et al.*, 1972). The feedback inhibition is probably dependent upon activation of the adenylyl cyclase-cyclic AMP mechanism of the mast cell via prostaglandin-specific adenylyl cyclase receptors. It seems clear that inflammation is the result of complex interaction between several different mediators.

The relationship of the anti-inflammatory action of corticosteroids to cellular changes in inflammation

In man, neutrophilia occurs 24 hr after a systemic dose of prednisolone. This seems to be related to a diminution of the marginal pool of neutrophils, especially in the lungs, which in turn is related to reduced granulocyte or possibly endothelial stickiness (Peters *et al.*, 1972). Whether the anti-inflammatory action of prednisone may be related, at least in part, to diminution of the local population of polymorphs in an inflammatory lesion seems to be uncertain, especially in view of the animal experiments of Willoughby and his colleagues referred to above, which suggest that at least in some laboratory animal models, neutrophils had no more than a minor role in delayed inflammation. There is also evidence listed by Ward (1966) that steroids in therapeutic concentrations can inhibit neutrophil chemotaxis.

The effect of corticosteroids on lymphocytes is complex, and has been the subject of a review by Claman (1975). Lymphopenia occurs after a single dose of prednisolone and this involves both B and T lymphocytes. The response of the remaining T lymphocytes to antigen and concanavalin A is impaired but both numbers and reactivity return to normal within 24 hr. The mechanism for steroid-induced lymphopenia is uncertain. Lymphocytolysis seems unlikely in view of the rapid return of the peripheral blood lymphocyte count to normal levels. Alternatively the lowered counts may be a result of redistribution of lymphocytes between blood and bone marrow. There is also some *in vitro* and *in vivo* evidence suggesting that corticosteroids in high dosage interfere with phagocytosis by macrophages.

The pharmacological actions of corticosteroids relevant to their actions as anti-inflammatory agents

An observation particularly familiar to derma-

tologists is the production of arteriolar vasoconstriction by potent glucocorticoids when applied topically. There is considerable evidence to indicate that the vasoconstrictor action of glucocorticoids is due not to a direct action but to sensitization of vascular muscle to noradrenaline. For example, guanethidine, which prevents release of noradrenaline from sympathetic nerve endings, prevents steroid vasoconstriction (Solomon, Wentzel and Greenberg, 1965). Independently of this, glucocorticoids have been found to antagonize the vasodilator actions of bradykinin and PGE. Thus it can be said that glucocorticoids modulate the response of the blood vessels to naturally-occurring vasodilator and vasoconstrictor agents. The explanation for this non-specific modulating action is unknown, but a plausible idea put forward by Bush (1962) suggests that glucocorticoids induce a conformational change in the receptor molecule thus preventing drug-receptor combination.

The actions of glucocorticoids at a biochemical level

One of the most exciting developments in our knowledge of the actions of anti-inflammatory drugs has been their actions on the prostaglandin synthesizing enzyme system. Prostaglandins are not normally found free or stored in tissues. They are synthesized locally in response to injury.

The pathway for biosynthesis of the 20-carbon fatty acids PGE and PGF is exemplified by the pathway for synthesis of PGE₂ and PGF₂α from arachidonic acid substrate. The source of this substrate is cell membrane lipid probably released as a result of the action of the lysosomal enzyme phospholipase.

The action of a mixture of enzymes present in the microsomal fraction collectively termed prostaglandin synthetase converts arachidonic acid to PGE₂ and PGF₂α by an oxygenation process. During the course of this reaction, intermediates are formed including peroxides and cyclic endoperoxides. These are extremely labile, having a half-life of less than 5 min and are therefore very difficult to study. However, it appears they are highly active pharmacologically and may be as important as PGE₂ and PGF₂α in the response to injury.

The important discovery made by Vane and his colleagues (Vane, 1971) was that the enzymic reaction could be inhibited by non-steroid anti-inflammatory drugs including aspirin, indomethacin and paracetamol, probably by blocking binding sites on the enzyme. He found that corticosteroids had little or no action on the enzyme. He concluded that the analgesic and anti-pyretic actions of these non-steroid drugs was due to their ability to inhibit prostaglandin synthetase. However, it has now become apparent that corticosteroids do have a

more complex inhibitory action on PG formation. The present author (Greaves and McDonald-Gibson, 1972) studied the effect of steroid and non-steroid anti-inflammatory drugs on prostaglandin synthetase from skin. Like Vane he found that if he used a purified enzyme preparation he obtained significant dose-related inhibition of synthesis by the non-steroid drugs and none by potent steroids such as flucinolone and betamethasone. By contrast, if a crude skin homogenate was used, it was possible to obtain convincing inhibition of PG biosynthesis by corticosteroids as well as by the non-steroid drugs.

It now seems from further work by others that steroids, although not inhibiting the synthesizing enzyme, may prevent the release of prostaglandins. Lewis has demonstrated inhibition of release of prostaglandins from adipose tissue undergoing functional vasodilation as a result of hormone-evoked lipolysis (Piper and Lewis, 1975) and Levine (Kantrowitz *et al.*, 1975) at Brandeis University, has shown that prostaglandin release from rheumatoid synovia is inhibited *in vitro* by steroids. Thus, both non-steroid and steroid anti-inflammatory drugs interfere with prostaglandin production in tissues in the response to injury although they act at different points in the reaction sequence.

Corticosteroids may of course have more than one action on the PG-synthesizing system. It has also been suggested that corticosteroids may act earlier on by preventing release by injury of the lysosomal enzyme phospholipase, whose activity seems essential for release of the prostaglandin forming substrate arachidonic acid as a prelude to prostaglandin biosynthesis.

This is an opportunity to consider the much argued problem of the relevance of the lysosomal membrane stabilizing properties of glucocorticoids described by Weissman (1969) to their supposed therapeutic mode of action. There is no doubt that corticosteroids have the ability to stabilize membranes. This has clearly been established for lysosomal and mitochondrial membranes by Chayen *et al.* (1970) and is probably due to formation of protein-steroid-phospholipid complexes. Some doubt has, however, been cast on the significance of this effect in relation to *in vivo* anti-inflammatory activity because of the lack of correlation between rank order of potency in lysosomal membrane stabilization and anti-inflammatory activity of steroids *in vitro*.

It must, finally, be pointed out that steroids are a unique class of anti-inflammatory drug in that they seem to inhibit most or all of the major components of inflammation. Thus, it is not surprising that separate

actions can be distinguished at cellular, pharmacological and biochemical levels. There are also a number of other probably important modes of action including a stimulatory action on the adenyl cyclase-cyclic adenosine monophosphate system and on histamine formation which have not been discussed here. Because of the toxic effects of available corticosteroids, new alternatives are badly needed. The difficulty with developing non-steroid anti-inflammatory alternatives to corticosteroids is that known classes of non-steroid anti-inflammatory agents possess a much more limited range of anti-inflammatory actions. Most effort is therefore being currently directed towards increasing the therapeutic index of existing steroids.

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