are always seeking to prove to their masters, who are ultimately the general public, that they are funding relevant research. It is up to investigators to generate good ideas and stimulate the enthusiasm of nascent research workers.

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References

Lipocortin: What Is It and What Does It Mean?

'Medical men don't know the drugs they use, nor their prices' Roger Bacon once rather acerbically remarked [1]. Although the latter is probably no longer true in these days of hospital trusts and General Practitioner budgets, it is an unfortunate fact that we are often sadly ignorant about the pharmacology of some of our most useful drugs. For example, look at aspirin or morphine: both have a long and venerable history but it is only recently that we have come to understand how they work, whilst other rheumatological drugs such as colchicine, gold and penicillamine continue to baffle us. Recent research has, however, shed light on the mode of action of those most potent of anti-inflammatory agents, the glucocorticosteroids.

It was of course through the efforts of a rheumatologist that hydrocortisone (and later its synthetic congeners) were introduced into clinical medicine in the first place. Phillip Hench believed that the reason why his female patients went into remission during pregnancy was because of elevated plasma levels of the hormone and his observation that administration of glucocorticoids reproduced this effect [2] overturned the dogma of the day which maintained that steroids had a pro-inflammatory role. To many, it may seem odd that the adrenal cortex should secrete a powerful anti-inflammatory hormone during injury, infection or stress, just when you might expect such a factor to be absent. Munck and his associates [3] have proposed that cortisol's function is to dampen down 'defence reactions' such as the release of β-endorphin, insulin, ADH, cytokines and so on, which also occur during such episodes and that if it were not for this counter-balancing influence, these defence reactions would dominate the physiology of the patient with harmful results. Following this line of reasoning it is easy to see why glucocorticoids are so effective: they are the signals which the body generates to moderate and modify the response to injury. But how exactly do they accomplish this?

It is now generally believed that most actions of steroids are brought about by changes in gene expression. When occupied by glucocorticoids, specific cellular receptors acquire the ability to bind regulatory elements on genes bringing about changes in the transcription and subsequently the translation of some key enzyme or protein [4]. A good example of a gene which is suppressed is that of the cytokine interleukin 1 [5]. It is easy to see how suppression of this (and indeed some other) cytokines can reduce inflammation but there are other mechanisms too. The synthesis of many proteins is increased by steroids and amongst these is an unusual and interesting protein which forms the topic of this editorial.

Lipocortin (also called annexin I) is a 37 kd member of a super family of at least ten related proteins and may be found in many cell types throughout the body especially in those of leucopoietic and epithelial origin [6]. The mechanism of steroid regulation is complex. Adrenalectomy leads to a fall in lipocortin mRNA in animals [7] and conversely administration of hydrocortisone to animals or man leads to the rapid (within 30–60 min) appearance of increased amounts of lipocortin I in cells such as peripheral blood monocytes of [8]. Although it does not contain a leader sequence (a molecular 'bar code' which enables cells to sort secreted proteins), lipo-
cortin 1 appears rapidly on the cell surface where it combines with a small number of high-affinity binding proteins [9] to bring about its biological effects. Because attachment to this binding protein is through a calcium-dependent mechanism it seems unlikely that lipocortin 1 is a circulating hormone although some secretory fluids (such as seminal plasma) do contain high concentrations [10].

Early investigations of biological activity were hampered by a lack of pure protein but lipocortin 1 has now been cloned [11] and following refolding, shows striking glucocorticoid-like activity in several models of experimental inflammation such as rat paw oedema [12], mouse neutrophil migration [13] and fever in rats or rabbits [14,15]. It also suppresses the generation of pro-inflammatory lipids by cells in vitro [16]. As yet there are no data available in man.

Some actions of glucocorticoids in experimental systems can be abrogated with anti-lipocortin 1 antibodies thus providing additional strong evidence for a mechanism dependent on induction of this protein [14]. There were early reports of anti-lipocortin 1 autoantibodies in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [17] and the presence of autoantibodies of the IgG and IgM type has now been confirmed in both groups [18]. In SLE the titre of the antibody appeared to correlate with the severity of the illness but in RA a more complex and potentially alarming disposition was observed. Patients who had not received oral steroid treatment were found to be free of autoantibodies but in those patients taking such medication a proportion of the population developed anti-lipocortin 1 autoantibodies. Interestingly, patients with high titres exhibited a marked degree of steroid resistance.

But what does all this mean for rheumatology? It is of course unrealistic to suppose that we will soon be treating our patients with high molecular weight proteins. The real importance of this finding is that it points to an endogenous mechanism, utilized by glucocorticoids, which acts to reduce inflammatory episodes. We must examine with care the biological actions produced by lipocortin 1 after combination with its cell surface binding protein and look for other, much shorter synthetic peptides (or, better still, other small molecules) which are able to mimic this action. If we can achieve this then we will have identified a way to produce some steroid-like actions without the heavy penalty of the side effects brought about by the other genomic actions of these hormones. And if Bacon’s ghost still haunts our hospitals and research laboratories perhaps we will be able to persuade him that we ‘unlearned apothecaries’ may still have a trick or two up our sleeves. Who knows?

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