CHAPTER 8

Glucocorticosteroids in Asthma

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A. Mechanism of Action of Glucocorticosteroids

The mechanisms by which glucocorticosteroids act to control asthma are unclear, partly because the underlying pathology causing this condition remains to be fully elucidated, and also because many of the actions of glucocorticosteroids are still unexplained. In particular, their anti-inflammatory effects are the most frequently harnessed by clinicians, but the least well understood. Glucocorticosteroids can cause certain cellular responses by direct interaction with cell membranes or, more commonly, they complex with specific receptors to modulate gene expression and protein synthesis. In the context of asthma therapy, steroid-induced protein synthesis may occur either in the respiratory tract, or elsewhere in the body, with secondary effects occurring in the airways. For example, stimulation by glucocorticosteroids of $\alpha$-proteinase inhibitor synthesis in the liver increases circulating levels of this protein and thus may modify the proteinase-antiproteinase balance of the airways and lungs.

Likewise down-regulation of interleukin-1 (IL-1) synthesis may also be important in resolving the inflammatory response in the airways (KNUDSEN et al. 1987).

One thing that can be stated with certainty is that steroids reduce practically every facet of airway inflammation and this makes a description of the totality of steroid actions very difficult indeed.

I. Induction of Protein Synthesis

Gluocorticosteroid receptors are found in most cell types (BALLARD et al. 1974). The interaction of glucocorticosteroids with the specific receptor induces a conformational change in the latter, which in turn permits it to interact with a specific region of the nuclear DNA, thereby regulating the production of complementary mRNAs and the proteins which they encode (see RINGOLD 1985 for a recent review). It is important to remember that not all genes which are modulated by steroids are up-regulated: many, for example the IL-1 gene, are down-regulated.

Glucocorticosteroids have been shown to induce the synthesis of a number of proteins. However, most of these regulate the metabolic effects of
glucocorticosteroids (Schutz et al. 1975; Iynedijian and Hanson 1977; Haynes and Murad 1985) rather than the anti-inflammatory actions which are believed to be important in the control of asthma. The action of some potentially anti-inflammatory proteins, the synthesis of which is thought to be glucocorticosteroid-modulated, is discussed below.

1. Lipocortins

The lipocortins are a family currently consisting of six member proteins which have differing molecular weights and N-terminal sequences (Pepinsky et al. 1988; Crompton et al. 1988). They share considerable sequence homology, their basic structure consisting of four or more repeats of a single sequence of about 70 amino acids. Interestingly, this primary structure occurs in a number of other proteins, known collectively as annexins (Geisow and Walker 1986) including the calpactins, calcimedins, calelectins, endonexins and chromobindins, all of which share the common property of binding calcium and phospholipid (Saris et al. 1986; Huang et al. 1986; Geisow 1986). Therefore, it has been suggested that this primary protein structure may facilitate the association of the proteins with membranes. Calcium ions are essential for this interaction and may form a “bridge” between phospholipid and protein moieties. However, there is recent evidence to suggest that there are a discrete number of saturable binding sites for at least one lipocortin (lipocortin 1) on the surface of some cell types but not others (Goulding et al., in press) and it is unlikely that this particular protein associates in a non-specific way with plasma membranes.

Since only one member of the lipocortin subfamily has been studied in depth worth respect to steroid-inducibility, the remainder of this section will focus on this protein, lipocortin 1. Lipocortin 1 has a molecular weight of 37 kDa and the gene encoding the human protein has been cloned (Wallner et al. 1986). The protein consists of 348 amino acids of which roughly 30% are charged, thus rendering it a highly polar molecule (Wallner et al. 1986). It has one potential glycosylation site, and several potential sites for phosphorylation. The significance of the latter will be discussed below. Interestingly, the protein has no leader peptide, even though it is found in extracellular fluids (Blackwell et al. 1982; Smith et al. 1990) and thus its mechanism of release from cells is currently unknown. Beyond these basic facts, almost every role or action suggested for this enigmatic protein by one research team has been disputed and rejected by another.

In this chapter, we suggest how lipocortin 1 may have some therapeutic role in asthma, and discuss our hypothesis in the light of the evidence to date. It is proposed that lipocortin 1 is glucocorticosteroid-regulated and that it is anti-inflammatory, suppressing inflammation possibly by down-regulating the activity of phospholipase A2 (PLA2), the rate-limiting enzyme for the production of the eicosanoid inflammatory mediators and platelet activating factor (PAF). PLA2 is also an important enzyme in the control of other