Chapter 19. Mechanisms of Action of Glucocorticosteroids

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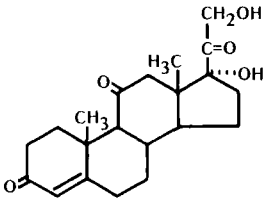
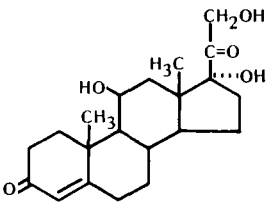
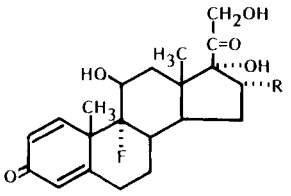
Introduction - Glucocorticosteroids display a variety of complex effects on different biologic systems and cell types. This review will focus on the mechanisms of action of these agents on inflammatory and immune responses, particularly with respect to human biology in vivo. Effects of glucocorticosteroids on vascular tissue, leukocyte kinetics and function, and various humoral factors involved in these responses will be considered. The structures of some typical corticosteroids are shown below.



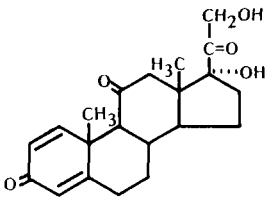
Cortisone



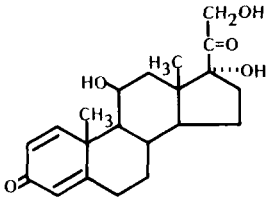
Hydrocortisone (Cortisol)



Triamcinolone (R=OH)
Dexamethasone (R=CH_3)



Prednisone



Prednisolone

Corticosteroid Receptors - The precise molecular mechanisms whereby corticosteroids exert their divergent effects are not well delineated at present. However, it has been demonstrated in a variety of models that many of the cellular and tissue effects of corticosteroids are triggered through an interaction with intracytoplasmic steroid receptors in the target cell.[1-3] The steroid-receptor complexes thus formed migrate to, and become associated with the cell nucleus. This leads to the synthesis of specific mRNA which, in turn, induces new protein synthesis. The newly synthesized protein may be an enzyme or an inhibitory protein, and it is highly likely that such a mechanism is responsible for the modulatory effect of corticosteroids on leukocytes involved in inflammatory or immune responses.[4,5]

Tissue and Vascular Effects - Inflammatory and immunologically mediated reactions are almost invariably associated with extravasation of fluid and cells from the intravascular compartment into surrounding tissues via leakage from capillaries and venules.[6]

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Clearly, corticosteroid administration inhibits the leakage of fluids and cells into inflammatory sites.[7] Several mechanisms for this effect have been proposed, the most obvious being vasoconstriction of the capillaries.[8,9] It is not presently clear how this effect arises; however, antagonism of vasoactive substances such as histamine,[9] kinins,[10,11] or plasminogen activator[12] have been suggested to be involved.

Kinetics and Traffic of Cells - Corticosteroid administration in man has profound effects on the distribution and circulatory properties of various populations of leukocytes.[13-17] The effect is transient and related to the dose and dose-interval of administered drugs.

Approximately 4 hours following intravenous administration of 100 to 400 mg of hydrocortisone or its equivalent to man, a dramatic, but transient, lymphocytopenia and monocytopenia occur, with a return to normal counts by 24 hours.[13,16,18] The mechanism of this cell depletion from the circulation is not a result of cell death, as is the case with corticosteroid-induced lymphopenia in corticosteroid-sensitive species, such as mouse, rat and rabbit. Rather, it is caused by a redistribution of these cells out of the circulation into other body compartments, such as bone marrow.[14,15] In fact, normal human mononuclear cells are extremely resistant to corticosteroid-induced lympholysis seen in mouse and rat.

The intravascular lymphocytes most susceptible to this redistribution belong to the recirculating pool of lymphocytes which, under normal circumstances, is in constant equilibrium with the extravascular lymphocyte pool in thoracic duct, spleen, lymph nodes, and bone marrow.[14,15] Although most identifiable subpopulations of lymphocytes are affected to some degree, corticosteroid administration selectively depletes thymus-derived (T) cells more than bone marrow-derived (B) cells[13,16,18] and, within the T cell population, cells with IgM-receptors are depleted to a greater extent than cells with IgG-receptors.[19]

The eosinopenia resulting from corticosteroid administration is also thought to result from a redistribution of these cells out of the circulation into other body compartments.[20]

The precise mechanism for the redirection of cell traffic is unclear. Cells normally enter and leave the circulation by migrating through the endothelium of the microvasculature. Complementary surface configurations and interactions between the circulating cells and the endothelial cells of the vessels probably influence entrance and egress of cells to and from the intravascular compartment.[15] It is uncertain whether corticosteroids exert their effects on the circulating cells or on the vascular endothelium. However, *in vitro* alteration of the lymphocyte surface configuration results in similar changes in circulation patterns following reinfusion of these cells.[21-25] This suggests that corticosteroids alter traffic patterns of cells by affecting their surface charge or receptors, thereby interfering with lymphocyte-microvascular interactions.

Corticosteroid administration also markedly influences neutrophil kinetics. The resulting granulocytosis is a consequence of multiple effects including enhancement of neutrophil release from bone marrow reserves, prolongation of neutrophil half-life, and inhibition of neutrophil migration into inflammatory sites.[17] It is this last effect which is closely linked to the anti-inflammatory effects of corticosteroids.

Corticosteroids inhibit the adherence of neutrophils to the microvascular endothelium of an inflammatory locus.[26] In addition, it has been shown that *in vivo* administration of corticosteroids results in decreased *in vitro* adherence of neutrophils to nylon wool columns.[27] Since one of the first recognizable events in the process of neutrophil influx into inflammatory loci is adherence of neutrophils to the vascular endothelium, it appears likely that inhibition of this intial step is an important mechanism in the interruption of neutrophil migration.

Functional Capabilities of Cells. To accurately delineate the effects of corticosteroids on various functional parameters of the different classes of leukocytes one has to distinguish between effects which are attainable *in vivo* and effects which cannot be achieved *in vivo* because they require suprapharmacologic drug concentrations.

The activities of corticosteroids both *in vivo* and *in vitro* on most recognizable cell functions involved in inflammatory and immunologic reactions have been described.[1,2,17,28,29,30] These include effects on cell activation, proliferation, and differentiation; expression of cell surface markers and surface receptor function; phagocytosis, lysosomal membrane stability, antigen processing, and microbial killing; and cytotoxic functions and response to soluble mediators. All of these functions can be suppressed by sufficiently high concentrations of corticosteroids *in vitro*. However, relatively few of these are affected by drug concentrations that can be achieved in man *in vivo*.[17] In contrast, the effects of corticosteroids on cell kinetics and migration patterns are elicited readily by concentrations that are achieved *in vivo*.[17]

If one compares the relative corticosteroid effects on the functional capabilities of the two major circulating phagocytic cells, the neutrophil and monocyte, it is clear that the monocyte is more susceptible to drug concentrations attainable *in vivo*. Not only are the circulatory kinetics of the monocyte sensitive to these concentrations, but functional properties, such as phagocytosis and microbial killing, are also impared.[31] Neutrophil phagocytosis and microbial killing are more resistant to corticosteroids at comparable drug concentrations.[17]

Cellular functions of lymphocytes such as occur during autologous mixed leukocyte reactions[32] and in the expression of suppressor cell activities[33,34] are particularly sensitive to physiologic concentrations of corticosteroids.

Despite studies showing corticosteroid-induced host defense effects, a low incidence of spontaneous infections has been reported in patients receiving corticosteroids.[17]

Effects on Humoral Factors - It is difficult to separate corticosteroid effects on humoral factors involved in inflammatory and immunologic reactions from effects on cellular functions since, in most cases, the humoral factors are cellular-derived. However, certain well defined humoral mechanisms are clearly influenced by corticosteroid administration.

Although antibody production, particularly secondary responses, are resistant to the effects of corticosteroids, total immunoglobulin synthesis can be suppressed by *in vivo* administration of high doses of corticosteroids.[35] Also, high doses of corticosteroids can result in a decreased level of serum complement components.[36] This effect is probably a manifestation of both decreased production and increased catabolism. Corticosteroids also can interfere with binding of certain immunoglobulins to the Fc receptor of certain cell types,[37,38] thus interfering with related functions such as phagocytosis and cytotoxic effector capabilities. Other potentially important effects of corticosteroids on humoral factor-related phenomena *in vitro* include inhibition of the response of macrophages to various lymphokines, particularly macrophage migration inhibitory factor,[39] and the interference with the response of neutrophils to soluble chemotactic factors.[40] The latter effect may be related to corticosteroid mediated inhibition of neutrophil adherence to vascular endothelium *in vivo*.

Summary - Corticosteroids can potentially interfere with virtually every phase of inflammatory and immunologic reactivity. Generally, kinetics and circulatory patterns of leukocytes are more sensitive to corticosteroid modulation than are functional effects of cells. In addition, various classes and subclasses of leukocytes appear to differ in sensitivity to corticosteroid effects. The precise mechanisms of their effects are still unclear. However, it is likely that they relate at least in part to specific receptor interaction of corticosteroid with the involved cells.

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