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Review

Corticosteroids: the mainstay in asthma therapy

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Abstract—Inflammation is now marked as a central feature of asthma pathophysiology and aims of current asthma management are not only to treat acute symptoms of wheezing, breathlessness, chest tightness, cough but also to suppress the underlying inflammatory component. Despite the availability of a number of drugs, corticosteroids remain the mainstay in the management of all types of asthma as these are the most potent and effective antiinflammatory agents available so far. Corticosteroids suppress virtually every step in inflammation. However therapeutic doses of oral glucocorticoids are associated with a range of adverse reactions. To overcome these side effects, inhalations have been developed to deliver glucocorticoids directly to the lungs and in the process a number of aerosol preparations have become available, which have advantage of significantly lower toxicity due to low systemic absorption from the respiratory tract and rapid inactivation. Despite considerable efforts by pharmaceutical industry, it has been difficult to develop novel therapeutic agents for asthma management, which could surpass inhaled corticosteroids. Currently the data favours using inhaled corticosteroids as monotherapy in the majority of patients in all kinds of asthma. If combination therapy is recommended to achieve additional control in severe asthma cases, other drugs such as β-agonists, antileukotrienes, theophylline, etc. are considered as adjunct therapies to corticosteroids. This review discusses the importance of corticosteroids as first line therapy for asthma treatment with the availability of inhaled corticosteroids for chronic treatment and oral formulations for treating acute exacerbations of moderate to severe asthma.

Contents

1. Introduction

Asthma is a chronic inflammatory disorder of the airways with a wide range of presentations from intermittent but mild symptoms to persistent symptoms with chronicity. Despite advancements in the treatment,

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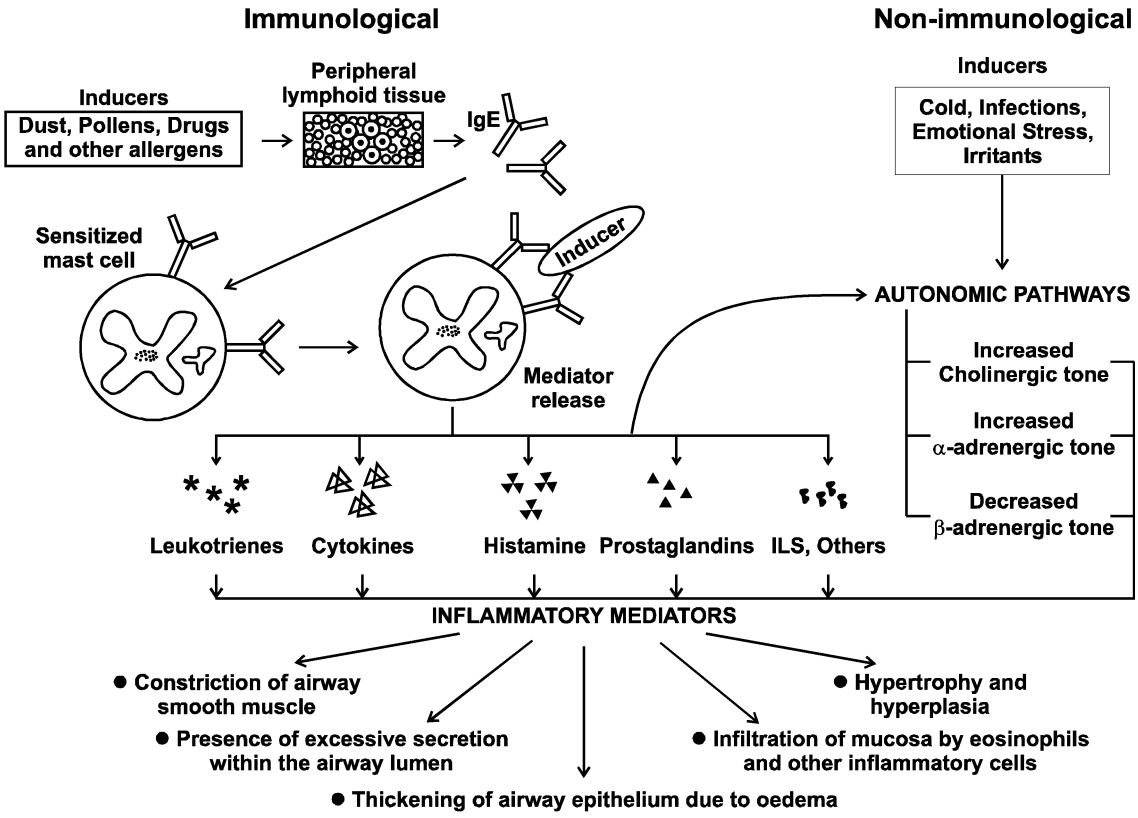


Figure 1. Pathophysiology of asthma.

asthma is rising in prevalence, severity and mortality affecting approximately 10% of children and 5% of adults worldwide.[1–4] Asthma is characterized by recurrent episodes of wheezing, breathlessness, chest tightness and cough, reversible airway obstruction and bronchial hyperresponsiveness to a variety of specific and nonspecific stimuli including allergens, histamines, chemical irritants, cold air and exercise.[5,6] With the understanding about the pathophysiology of asthma, the original belief that asthma is associated with isolated acute episodes of bronchospasm resulting from wide variations in resistance to flow in the airways has changed and it is now recognized as an inflammatory disorder.[7,8]

2. Asthma: an inflammatory disease

During the past decades, enough evidence demonstrating that asthma is primarily an inflammatory airway disease in which lung inflammation leads to airway obstruction has accumulated.[9–11] The features of the inflammatory process in asthma are complex, involving an interplay of events leading to hyperresponsiveness of the airways.[6] Immunological and nonimmunological mechanisms leading to asthma are depicted in Figure 1. The immediate pulmonary response following exposure to allergens is bronchoconstriction, which generally develops due to the activation of mast cells by specific antigens through cell-bound IgE[4] resulting in the release of histamines and synthesis of cysteinyl-leukotrienes (cys LTs). These acute phase mediators cause airflow obstruction by directly increasing airway tone. Mast cells also release proteases (e.g., tryptase, stromolysin and chymase) and many pro-inflammatory cytokines [e.g., tumour necrosis factor-alpha (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukins IL-3-5, IL-13 and chemokines], which contribute to airway inflammation and airway hyperresponsiveness[4,12] (Fig. 1). Thus on activation, epithelial cells, mast cells, eosinophils, neutrophils, macrophages and fibroblasts release a wide range of inflammatory mediators including histamine, proteases, growth factors, platelet activating factors, cytokines and leukotrienes, which leads to bronchospasm, airway hyperresponsiveness, airway smooth muscle hypertrophy,[4] denudation of basement membrane, mucus hypersecretion and activation of sensory nerves, all of which contribute to the pathophysiology of asthma.

2.1. Existing therapies for asthma

The main approaches towards the management of asthma are mainly based on both the pharmacologic and nonpharmacologic prevention. Avoidance of exposure to allergens[6] and other triggers of acute exacerbations are the major component of nonpharmacologic management whereas the pharmacological management of asthma is by use of drugs.[13] Although the available drugs for asthma are effective and well tolerated in majority of patients but still there is need for safer, effective and orally active bronchodilators and antiinflammatory agents.[1–4,8,13–15] Various types of antiasthmatic

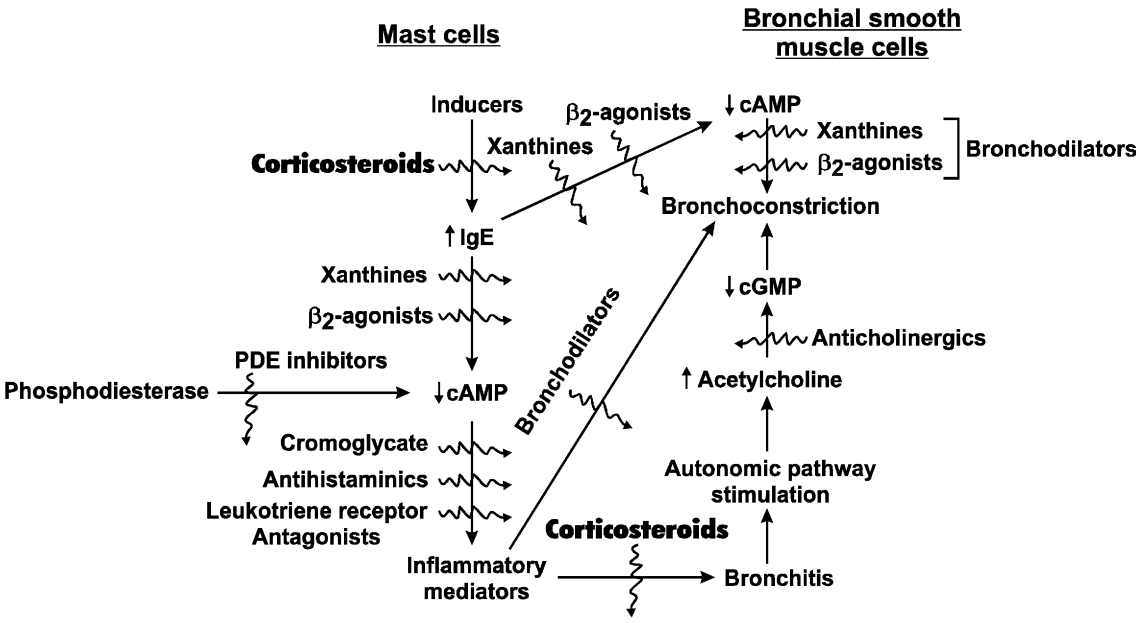


Figure 2. Different classes of antiasthmatic agents along with their mechanism and site of action.

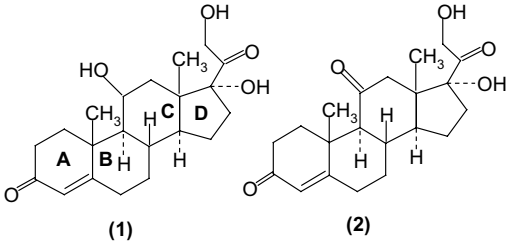
agents along with their mechanism and site of action are shown in Figure 2.

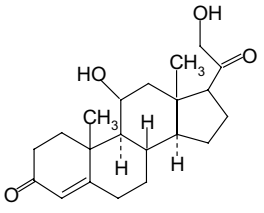
Bronchodilators relax airway smooth muscles and end an episode of asthma.[10] However these agents do not have an effect on airway inflammation. Until recently asthma therapy has principally emphasized the use of bronchodilators but a greater understanding of the central role of inflammation in the pathogenesis of asthma has led to a reevaluation of the use of antiinflammatory agents in the management of asthma.

2.2. Corticosteroids in asthma therapy

Shortly after their discovery, corticosteroids became the cornerstone of asthma treatment. Steroids have been associated with the treatment of asthma since 1949, when patients were first treated with adrenocorticotropic hormone (ACTH).[14] These are the most potent and effective agents available for the treatment of asthma because of their excellent antiinflammatory profile. Corticosteroids reduce the morbidity during severe acute attacks, reduce inflammation and aid the restoration of pulmonary function.[15] Development of steroid molecules with increased selectivity for the glucocorticoid receptor led to the development of orally active antiinflammatory glucocorticoids.[16] These drugs are still in use today particularly in patients with severe asthma.[17] However, therapeutic doses of oral glucocorticoids are associated with a range of adverse reactions, which prevent steroids from being the ideal therapy for allergic asthma. Therefore inhalation glucocorticoids have been developed in an attempt to reduce systemic side effects.[18] The introduction of inhaled preparations and the revelation of asthma as an inflammatory disease make this class of drugs as the most suitable for treatment of asthmatic patients.[19–23]

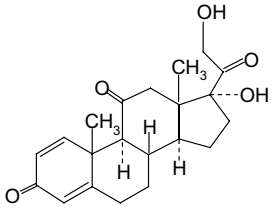
The antiinflammatory activity of hydrocortisone (**1**), cortisone (**2**) and corticosterone (**3**), isolated from adrenal glands, was demonstrated way back in 1930s and 1940s.[15]





The major drawback of this therapy was systemic side effects of glucocorticoids, which include adrenocortical suppression, bone thinning, muscle wasting, thinning of skin, cataracts, decreased growth in children, facial rounding, fluid retention, decreased glucose tolerance, increased blood pressure and acne. It was established that the key structural features required for the antiinflammatory activity include the 3-keto group, double bond between 4,5-position and presence of 11-hydroxyl, 17α-hydroxyl and 21-hydroxyl groups. Number of attempts were made to synthesize numerous analogues of cortisone possessing antiinflammatory activity with

improved therapeutic index[15,24] and initial breakthrough came with the introduction of 1,2-double bond in A ring of steroid nucleus giving prednisone (**4**) and prednisolone (**5**). These were four times more potent as antiinflammatory agents



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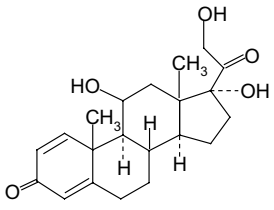

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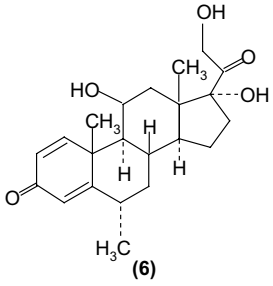
than hydrocortisone along with lower mineralocorticoid properties. Introduction of 6α-methyl and 9α-fluoro group in **5** gave the compounds methylprednisolone (**6**) and triamcinolone (**7**), respectively.[25,26]



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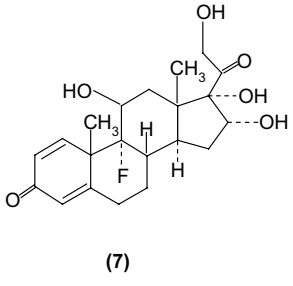
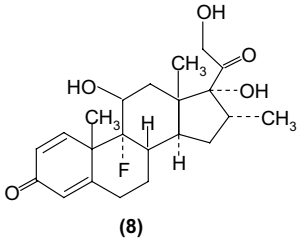


(7)

These agents provided further separation of the antiinflammatory and mineralocorticoid properties. Replacement of 16α-OH group with 16α-methyl group afforded dexamethasone (**8**), its 16β-isomer betamethasone (**9**) was found to be a potent antiinflammatory agent devoid of mineralocorticoid properties.[16,24]



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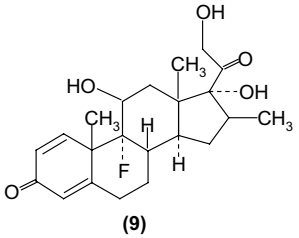

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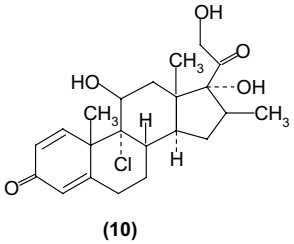
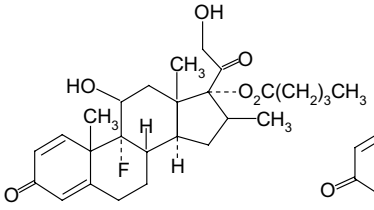
Further the replacement of 9α-fluoro group in **9** with 9α-chloro gave the compound



(10)

beclomethasone (**10**).[27] Still the separation of antiinflammatory activity from other side effects was not completely achieved and the use of topically active steroids via inhalation to reduce completely the systemic side effects was investigated. It eventually became the breakthrough therapy for asthma. As far back as in 1950s inhaled hydrocortisone (**1**) and cortisone (**2**) were tried but the initial trials for the management of asthma were made with carboxylate esters, betamethasone valerate (**11**) and beclomethasone dipropionate (**12**).[27] The response observed with these inhaled topical steroids was better than that with inhaled hydrocortisone. Discovery



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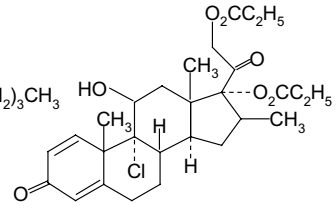
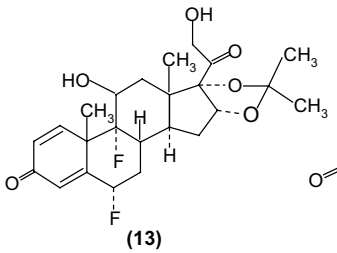


(12)

of beclomethasone dipropionate (**12**), an effective inhalation corticosteroid[28] with limited systemic distribution was a major achievement.

Further research in this area led to the development of fluocinolone acetonide (**13**), flunisolide (**14**) and fluocortin butyl ester (**15**) as antiinflammatory agents. Nasal spray of flunisolide, a 16α,17α-ketal androstane derivative is effective in allergic rhinitis in clinical use.[24,29,30] Their protective effects in patients with bronchial asthma has been studied. Clinical data showing good protective effects of fluocortin butyl ester in patients with bronchial asthma is available.[31] Efficacy and safety of a new metered-dose inhaler of flunisolide has recently been reported.[32] A desirable property for corticosteroids to be used safely in asthma is their rapid systemic metabolism so that least systemic effects are produced. Thus a clear need exists for topically potent antiinflammatory



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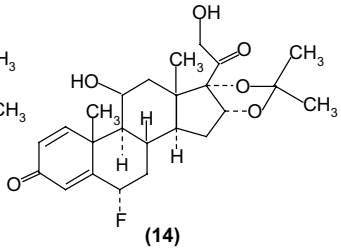

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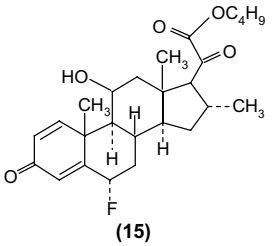
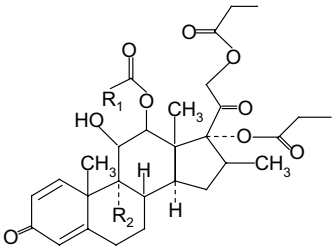


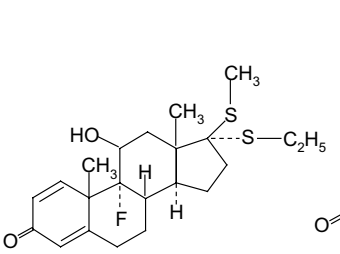
(15)

agents, which either are not systemically absorbed or undergo facile systemic metabolism to inactive compounds. In the former vein, it is found that the introduction of a hydrophobic 12β-acyloxy group into bromo betamethasone 17,21-dipropionate or beclomethasone 17,21-dipropionate resulted in novel, topically potent structures (**16**–**21**) that are not systemically absorbed.[33]



	R_1	R_2
(16)	CH_2CH_3	Br
(17)	$CH_2CH_2CH_3$	Br
(18)	$CH_2CH(CH_3)_2$	Br
(19)	C_6H_5	Br
(20)	CH_2CH_3	F
(21)	CH_2CH_3	Cl

Unfortunately their protective effects against bronchial asthma were not very encouraging. Success in the latter approach has been reported for androstane 17-thioketals (tipredane) (**22**)[34] and 17β-carboxyandrostane esters (**12**).[35–37] Esterification of both the 17α-hydroxy and 17β-carboxylic acid functions resulting in the formation of 17α,17β-dipropionates and also 17β-fluoromethylcarboxylates showed high topical antiinflammatory activity with weak undesirable side effects.[38] Rapid deactivation by cleavage of propionate groups results in negligible side effects. Halomethyl esters of androstane-17β-carbothioic acids were also reported with potent and novel corticosteroidal activity and promising separation of activity.[39] This led to the discovery of most recently introduced glucocorticoid, fluticasone propionate (**23**)[18,39–41] for inhalation use in asthma. This compound has been developed with advantage of lower systemic side effects due to low oral bioavailability and high potency and is the current first line therapy in US and Britain. Antileukotrienes is the only new class of asthma treatment other than corticosteroids to have been licensed in the last 30 years. Montelukast, an orally dosed leukotriene D_4 receptor antagonist is the most competitive agent from this class of antiasthmatics. Both montelukast and fluticasone (**23**) improve pulmonary function and provide clinical benefit to patients with chronic asthma.[5,42] Though montelukast has a faster onset of action, its exact role in clinical situation remains to be established. Whereas inhaled steroids produce better lung functions and quality of life as well as reduced symptoms. A recent comparative study implies the use of montelukast as an additional therapeutic option along with inhaled corticosteroids, especially in view of their possible complementary effects on reducing airway inflammation.



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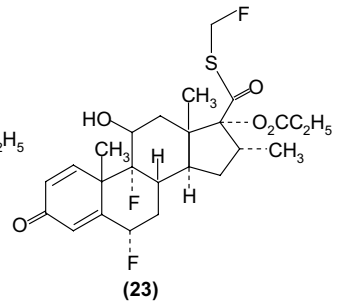
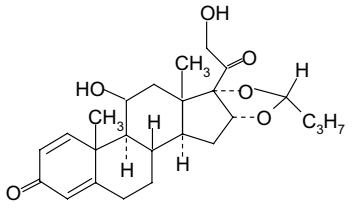


(23)

In 16,17-acetal series, new generation nonhalogenated glucocorticoids like budesonide (**24**)[18,43] with high local antiinflammatory properties is the new entry for inhalation use in asthma. These agents are also being developed with the advantage of lower systemic side effects because the dose used for inhalation is much less to produce side effects.

Latest to be introduced in this series is a soft steroid ciclesonide (**25**) developed at Atlanta.[44,45] It is an ester prodrug essentially devoid of oral bioavailability, which is activated upon activation of endogeneous esterases. Its advantages include targeted activation in the lung and prolonged duration of action. This drug is in phase III clinical trials for asthma treatment and is awaiting FDA approval for marketing in US.



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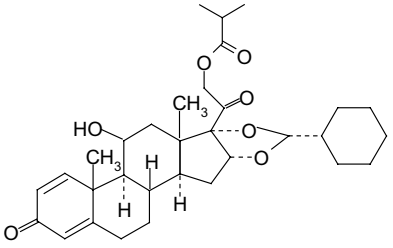

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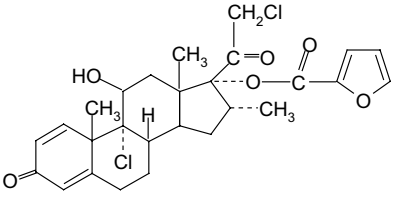
Recently nasal spray of mometasone furoate (**26**) has been approved for marketing by the United States



(26)

Food and Drug Administration for use in asthma.[46,47] All these drugs differ markedly in their affinity for the glucocorticoid receptors with fluticasone and budesonide having much higher affinity than beclomethasone.

2.3. Molecular mechanism of steroid action

Corticosteroids alleviate major symptoms of asthma by reducing airway reactivity while restoring the integrity

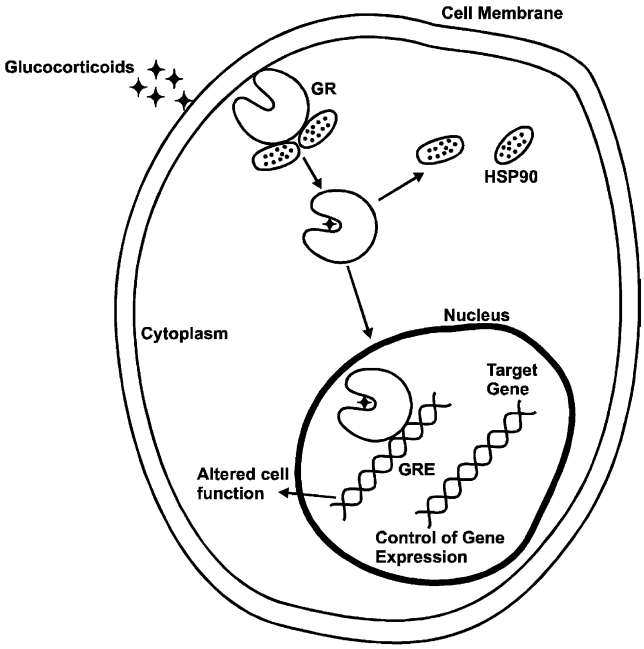


Figure 3. Control of gene expression through the glucocorticoid receptor signalling pathway.

of the airways, however, the mechanism of action used to achieve these effects is not fully understood.[1] In the past decades, great progress has been made in understanding the cellular biology and antiallergic and antiinflammatory mechanisms of corticosteroids. Corticosteroids enter the cell via passive diffusion through the plasma membrane[48] where it binds to soluble class specific glucocorticoid receptors (GRs), which are present in cytoplasm of respiratory cells[49] and only on binding of the glucocorticoid does it move into the nuclear compartment[50,51] (Fig. 3). Glucocorticoid receptors are expressed in all cell types but predominantly in airway epithelium and endothelium of bronchial vessels.[52] The inactivated GR is bound to a protein complex of molecular chaperones including two subunits of heat shock protein hsp90[53,54] and a 59-KD immunophilin[55] protein, which prevent the unoccupied GR from translocating from the cytoplasm to the nucleus. It appears that hsp90 is necessary for ligand binding to GR and it may facilitate its proper folding into a conformation that is optimal for binding.[56] After binding with the glucocorticoid, the steroid receptor complex dissociates from heat shock protein and allow the translocation of the GR to the nucleus.[57–59] The steroid binding portion of the GR is at the carboxy-terminal end of the molecule. The GR contains two zinc fingers that bind to DNA after interaction with steroids. Several domains within the GR are important for transactivation of transcription, once the molecule has moved to the nucleus. Upon activation glucocorticoid receptor forms a dimer, which binds to DNA at sensus sites termed as glucocorticoid response element (GRE). Once binding has occurred transcription of DNA to mRNA and transcription into peptides and proteins takes place by the standard mechanism. Corticosteroids can activate some genes and repress others thereby inducing the synthesis of some proteins and inhibiting others, thus regulating the activity of biologically important molecules. GR may also interact with other transcription factors via leucine zipper interactions.[60–62] Indeed these interactions are central to the antiinflammatory effects of glucocorticoids. Corticosteroids may be effective in controlling asthma by inhibiting several aspects of the inflammatory process through increasing or decreasing gene transcription.[63] Although it is not yet possible to be certain of the most critical aspects of steroid action in asthma, it is likely that steroid decrease the accumulation and activation of inflammatory cells in asthmatic lung probably via cytokine associated mechanisms. Many cytokines involved in asthma exert their effect through NF-kB.[64–66] The GR, once bound to glucocorticoid, is capable of binding NF-kB and preventing its translocation to the nucleus. In addition glucocorticoids may directly increase the production of the inhibitor of NF-kB. Interactions have also been described with AP-1, a transcription factor particularly important for activation of lymphocytes by IL-2.[49] Corticosteroids may decrease the number of inflammatory cells, including mast cells, lymphocytes and eosinophils in the bronchial wall and also down regulate migration of eosinophils, block neutrophil adherence, macrophage function and diminish microvascular leakage. These effects are associated with the inhibition of cytokine production.[67–69] Corticosteroids also have been shown to inhibit the production of IL-1-6, IL-8, tumour necrosis factor alpha (TNF-α), granulocyte-monocyte colony-stimulating factor (GM-CSF), gamma-interferone and fibroblast growth factors. Steroids decrease the synthesis of arachidonic acid derived inflammatory mediators and PAF in many cell types, which is the key factor leading to decrease in the hyperreactivity. Steroids also decrease the mucus formation and also have been shown to inhibit the PG production in vitro and in vivo. Other interactions between GR and transcription factors include signalling from β_2 agonists via the cyclic AMP response element and the cyclic AMP response element-binding protein, although the clinical effect of these interactions in asthma is less certain.

2.4. Pharmacokinetics

The pharmacokinetic properties of currently available inhaled steroids account for their lower toxicity. After inhalation, an appreciate fraction of the dose (80–90%) is deposited on the oesopharynx and swallowed. It is then available for absorption into the systemic circulation through the liver and rapidly inactivated when it undergoes first pass metabolism in the liver.[70] Absorption of unmetabolized drug through the respiratory mucosa accounts for most of the systemic side effects of inhaled corticosteroids. The use of spacers in delivery device may further increase efficacy of these agents or lowering of the dose.[71] Fluticasone and budesonide have very efficient first pass metabolism in the liver so that less of these drugs reach the systemic circulation. It is calculated that for a steroid with 90% first pass hepatic

metabolism, approximately 75% of the total systemic availability originates from the lung absorbed fraction, and that mouth rinsing after inhalation enhances this figure to approximately 90%. Available information indicates that the newer corticosteroids possess lower oral bioavailability as in case of fluticasone.[72] The systemic availability is also a consequence of the method used for administration. The use of spacer and pressurized metered-dose inhalers in delivery device systems may further increase the efficacy of these agents or allow lowering of the dose.

2.5. Adverse reactions

While the incidence of side effects associated with inhaled corticosteroids is lower than that with oral formulations, some local and systemic adverse effects do occur.

2.6. Local side effects

Local side effects of inhaled steroids depend on the delivery system, dose and frequency of administration. The most common local side effect is dysphonia (hoarseness), which effects one-third of patients[73,74] and is reversible after discontinuation of treatment. Dysphonia is due to local irritation and is most likely to occur in individuals who speak frequently and at high volume.

Oropharyngeal candidiasis (thrush) affects adults more often than children[43,75] due to formation of colonies of the *Candiasis albicans*. The incidence of oral candidiasis is related to total daily dose of inhaled steroid[76,77] and it may be frequent, if inhaled steroids are used four times daily instead of twice daily although this has not always been observed. Clinical thrush is seldom a major problem; it can be controlled with nystatin or amphotericin B and rarely necessitates withdrawal of the inhaled steroid. Sore throat, throat irritation and cough are also common symptoms associated with the use of inhaled steroids.[74] These symptoms may be due to additives such as surfactants, which are found in steroid dose inhalers.

2.7. Systemic side effects

Systemic side effects of an inhaled steroid will depend on several factors including dose delivered to the patient, the pharmacokinetic fate of the particular inhaled steroid, the site of deposition of the drug and individual differences in steroid response between different patients and is potentially a major problem with long-term use of oral corticosteroids. The total systemic effect of a corticosteroid depends upon the drug deposited in the intrapulmonary airways and the amount absorbed from gastrointestinal tract.

Treatment with corticosteroids may cause hypothalamic-pituitary adrenal (HPA) axis suppression by reducing corticotropin (ACTH) production,[78] which in turn leads to reduced cortisol secretion by the adrenal gland. Oral and topically applied corticosteroids may affect the skin producing telangiectasiae, thinning easy bruising and striae due to structural alterations in the dermis, which becomes thin[79,80] because of the loss of extracellular ground substance that normally occupies the space between collagen fibres. Steroids also inhibit collagen synthesis.[80] Steroids can also induce osteoporosis by increasing bone resorption and decreasing bone formation.[81,82] Large proportions of patients receiving long term oral steroids experience rib or vertebral fractures.[83,84] Treatment with inhalation steroids has been shown to retard growth[85–88] even at doses as low as 2.5 and 5 mg prednisolone per day.[89–91] The suppressive effects seems to depend upon the duration of treatment, dose and frequency and when treatment is stopped catch-up growth may occur.[50] However growth retardation caused by daily and alternate day administration of large doses of systemic corticosteroids for extended periods of time may be permanent.[92,93] Prolonged administration of high doses of inhaled steroids increase risk of subcapsular cataracts.[92] Other side effects of systemic corticosteroids include weight gain, facial rounding, fluid retention, hypertension, myopathy, glucose intolerance, immune dysfunction and a range of mood and behavioural changes.[1,93]

2.8. Steroid resistant asthma

Although most patients with asthma respond to steroids, but there is a small proportion of asthmatic patients who fail to respond to even high doses of oral corticosteroids.[94] Monocytes and T lymphocytes isolated from these patients have impaired response to glucocorticoids in vitro. Some investigators have made attempts to divide steroid resistant (SR) asthma into two distinct type 1 and type 2 SR asthma. In type 1 SR asthma there is reduction in the affinity of the GR for steroid and this can be mimicked by incubation of T cells with IL-2 and IL-4,[95] which leads to a functional inhibition of glucocorticoid action.[96]

Type 2 SR asthma is associated with a marked reduction in the number of activated GRs within the nucleus after exposure of mononuclear cells to glucocorticoid in vitro compared to cells from normal individuals and glucocorticoid-sensitive asthmatics.[97] However, there is an evidence that in these patients there is hyperactivation of AP-1[98,99] and elevated activity of an enzyme c-*Jun* NH_2^- terminal kinase (JNK),[100] which activates AP-1 by phosphorylating its components. The enhanced activity of the cytoplasm prevents GR interaction with other proteins, resulting in glucocorticoid resistance. This resistance will be seen at the site of inflammation where cytokines are produced, that is, in the airway of asthmatic patients but not at noninflamed sites. GR expression and hence function may be regulated by several factors.[101] Down regulation occurs after exposure to glucocorticoids.[102] A marked reduction in GR mRNA occurs in human lung after exposure to corticosteroids

in vitro for 24 h[103] but it is not certain whether this persists after prolonged treatment in man.[104]

2.9. Inhaled corticosteroids

During recent years the development of inhaled corticosteroids heralded a new era in the treatment of chronic asthma.[93] Inhaled glucocorticoids are the most effective therapy for asthmatic patients. Due to airway inflammation present even in patients with mild asthma, therapy with inhaled glucocorticoids is now recommended as a first line treatment.[105] Beclomethasone dipropionate (Beclovent), triamcinolone acetonide (Azmacort), flunisolide (Aerobid), budesonide (Pulmicort), fluticasone propionate (Flovent) and mometasone (Asmanex) are the steroidal compounds already in clinical use as inhaled medication for asthma treatment in United States.[106] The advantage of these drugs is that the inhalation delivers the drug directly to the area of pathology with a very little systemic absorption and consequent side effects. These drugs are more effective than oral steroids in reducing bronchial hyperresponsiveness. Paediatric studies have demonstrated improved pulmonary function and symptoms, when these agents are tested in young and old children across the spectrum of asthma severity.[1,32,107] These improvements diminish when inhalation corticosteroids (ICSs) treatment is discontinued. It has been hypothesized that inhaled corticosteroids prevent deterioration in living function due to airway inflammation. Different inhaled corticosteroids differ in their potency, though there is little evidence of a difference in efficacy at recommended doses. Of those widely used by inhalation, flunisolide is less potent than beclomethasone while budesonide is more potent and fluticasone still more. The ability to use fewer inhalations with more potent drugs might enhance compliance.[108]

A variety of ICSs agents are now available; differences are predominantly related to the potency of the agent and the method of delivery. Traditionally propellant-driven metered-dose inhalers were used, which are now joined by dry powder inhalers activated by patient's own breath. Dry powder inhalers eliminate the need for a spacer device and some preparations deliver a higher fraction of medication to the airways. Other future developments include the replacement of chlorofluorocarbons with new propellants in metered-dose inhalers, which may improve delivery of the active agents.[109] Enthusiasm for ICSs has been tempered by concern about potential side effects. It has been observed in trials that 1.0–1.5 cm per year growth suppression[110] is seen using moderate to higher doses. Development of cataracts have only been described in adults,[111] but association has generally not yet been observed in trials of ICSs at moderate doses, although the response of hypothalamic-pituitary axis is unpredictable for the individual patients.[112] It is now clear that inhaled steroids are now appropriate first line treatment for patients who need almost daily inhalation therapy with β_2-adrenergic agonists as recommended by the International consensus on asthma.[113] Recently some investigators proposed inhaled steroids for patients with milder asthma and stressed the importance of early start to avoid possible irreversible airway obstruction, mainly in children.[114] However, there is a need to balance the potential for adverse systemic effects with the expected benefits.

3. Conclusions

Presently asthma, a common respiratory disorder, is recognized as an inflammatory illness, which results into bronchial hyperreactivity and bronchospasm. Antiinflammatory agents are prerequisite for the long-term management of chronic asthma. Even though recent trends in the design of new antiasthmatic agents include PDE-4 inhibitors, inhibitors of biosynthesis of IL-4, IL-4 antagonists, lipoxigenase and leukotriene inhibitors, thromboxane A_2 receptor antagonists, potassium channel openers and monoclonal antibodies, corticosteroids remain the main stay in asthma therapy because of their excellent antiinflammatory properties. Though antileukotrienes are currently being studied as alternative first line agents in mild to moderate asthma, their role in paediatric asthma is still unclear and their exact role in clinical situation remains to be established. Inhaled corticosteroids produce better lung function and quality of life as well as reduced symptoms in comparison with antileukotrienes. Glucocorticoids act by binding to a specific glucocorticoid receptor (GR) that upon activation, translocates to the nucleus and either increases or decreases gene expression. Identification of prescribed mechanism by which glucocorticoids act may remain new targets for the development of steroid drugs that may dissociate the antiinflammatory actions of glucocorticoids from their side effects due to gene induction. Novel therapeutic corticosteroids effective in most asthmatics have been developed to overcome the systemic side effects, which initially limited their usefulness. Inhaled corticosteroids are considered as the most significant aspect of safe asthma therapy. Recent trials continue to support the role of inhaled corticosteroids as the most effective therapy to control airway inflammation associated with persistent asthma. Contemporary asthma management guidelines also list these agents as controller medications with inhaled fluticasone propionate as the most effective agent available so far. Other antiasthmatics, if required for additional control of asthma are to be used as adjunct therapy to corticosteroids, which remains the first line treatment in the management of all grades of asthma.

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Biographical sketch

Dr. Ranju Gupta was born on 29th February 1968. She obtained her B. Pharm and M. Pharm degrees from Panjab University Chandigarh, India and was awarded the Ph.D. degree in 1996 from the same university under the supervision of Prof. D. P. Jindal. She joined as a lecturer of Pharmaceutical Chemistry at University Institute Pharmaceutical Sciences, Panjab University in 1996 and is presently working as a senior lecturer in the same institute. She is a life member of many professional bodies like IPA, IPGA and APTI, India. She has published many research papers in reputed journals and has presented her work at various national and international conferences.

Her main areas of research include synthesis and study of newer chemical moieties of diversified medicinal significance such as antiasthmatics, cardiovascular agents and heterosteroids. She is an active researcher and is presently working on two major research projects funded by HSCST and UGC, India.

Late Professor D. P. Jindal was born on 5th March 1942. He obtained his B. Pharm and M. Pharm degrees from Panjab University Chandigarh, India and was awarded the Ph.D. degree in 1975 from the same university. He joined as a lecturer in Department of Pharmaceutical Sciences, Panjab University in 1972 and got elevated to the position of Professor of Pharmaceutical chemistry in 1989. He was awarded Commonwealth Academic staff fellowship in 1980 to visit University of Strathclyde, Scotland, UK. He was a member of Pharmacy council of India and Drug Technical Advisory Board, India. He was on expert panel of various committees of AICTE, UGC and CSIR in the field of Pharmaceutical Sciences.

He excelled in the synthesis of heterosteroids and was associated in the discovery of Chandonium Iodide (Candocuronium Iodide), a potent NMJ blocker.

He was an active researcher with over 100 publications and has 18 patents to his credit. He left for heavenly abode on 1st June 2002.

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