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Glucocorticoids: The anti-inflammatory agents

K. K. Mishra and H. P. Pandey

Four decades have passed since the discovery of anti-inflammatory effects of glucocorticoids, yet the function of these compounds has remained an enigma and eluded the scientific community. However, glucocorticoids exert profound suppressive effects at almost every step of inflammation and they have a significant therapeutic role in medical practice. This article is an attempt to give a generalized account of glucocorticoid action at a molecular level.

One of the most important effects of glucocorticoids was discovered almost by chance in the late forties when it was observed by Hench *et al.*[1] that administration of cortisone reduced the severity of disease in patients suffering from rheumatoid arthritis. This discovery led to the Nobel prize for medicine in 1950, and called global attention to the anti-inflammatory effects of glucocorticoids. Since then, four decades have passed yet the anti-inflammatory effects of glucocorticoids are still not fully understood and are ruled out by some as pharmacological side-effects[2], produced by overdoses of hormone. Virtually it was Hench who in 1929 noticed that the condition of his patients with rheumatoid arthritis improved if they became pregnant or jaundiced. He thought that it might be due to a hormone from the adrenal cortex but he had to wait till 1949 to test his hypothesis when he with his colleagues synthesized cortisone. Administration of cortisone brought about rapid relief of the symptoms of rheumatoid arthritis[3]. For this remarkable achievement, Hench and his associates, Kendall and Reichstein, were jointly awarded the Nobel prize.

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Inflammation and its mediators

Inflammation, stated to be an essential prelude to healing, is the response of living tissues to injury. It is characterized by redness, heat, swelling, pain and loss of function. Redness and heat are the manifestations of increased circulation resulting from vasodilation. Swelling results from collection of protein-rich exudates because capillaries and venules become leaky to protein due to vasodilation. Chemical products formed after injury produce pain. When microorganisms breach local defences at skin and mucosal surface, systemic reactions are set off to destroy the foreign invaders, which result in inflammation. Inflammation mainly stems from the effects of mediators involved in the body's defence mechanism[4,5]. Immediately after injury, the white blood cells rush to the site of injury to protect the

body against foreign intruders which are called antigens. Vasodilation serves to increase blood flow to the injured site so that an increasing number of white blood cells reach there to check and destroy antigens[6]. Increased circulation provides more oxygen and nourishment to cells at the site of damage and helps removal of toxins and wastes. Inflammation is triggered and sustained by certain mediators coming from different sources[7]. Prostaglandins and leukotrienes are released from vascular endothelial cells and macrophages[8]. Histamine and serotonin produced by mast cells and platelets mediate the inflammation[9]. However, prostaglandins and leukotrienes have a central role in inflammation[10]. They are derived from a 20-carbon polyunsaturated fatty acid called arachidonic acid. Prostaglandins cause vasodilation and provide vascular permeability by enhancing the action of histamine and bradykinins[11]. They produce hyperalgesia (increased sensitivity to touch) by sensitizing the extreme nerve endings of pain fibres. Leukotrienes increase the permeability of microvasculature and they attract white blood cells and increase their adherence to endothelium[12]. Liberation of arachidonic acid from phospholipids of plasma membrane is the rate-limiting step for the generation of prostaglandins and leukotrienes[13]. The enzyme phospholipase A_2 (ref. 14) converts arachidonic acid precursor into arachidonates. Free arachidonic acid is then oxidized by two cytosolic enzymes, cyclooxygenase and lipoxygenase (Figure 1). These oxidations yield end-products, prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs) and other derivatives of hydroperoxy fatty acids[15]. Oxidation of arachidonic acid by cyclooxygenase pathway results in the formation of endoperoxide PGG_2, which is then reduced to PGH_2 with the release of reactive oxygen species. PGH_2 is converted in different cells into different prostaglandins and thromboxanes end-products (Figure 1). The inflammatory mediator effect of PGE_2, the major prostaglandin formed by granulocytes and monocyte/macrophages, is still unclear[16].

Anti-inflammatory role

Administration of glucocorticoids in large doses prevents full expression of the inflammatory reaction that is normally called forth by obnoxious agents[17]. It seems probable that the major cause of vasodilation and increased endothelial stickiness is the local release of prostaglandins[18]. Excessive amounts of glucocorticoids suppress the formation of both classes of compounds by inducing the synthesis of a large peptide inhibitor of phospholipase A_2, called lipocortin or macrocortin[19-21]. Thus both the cytosolic enzymes, cyclooxygenase and lipoxygenase, are deprived of substrate. Non-steroidal anti-inflammatory drugs such as endomethacin and aspirin check cyclooxygenase pathway and thereby prostaglandin synthesis, but leukotrienes synthesis is unaffected because lipoxygenase pathway is not blocked.

According to Dahlen *et al.*[22] the leukotrienes play a dramatic role in hypersensitivity and inflammatory responses. In leukocytes, lipoxygenase catalyses the formation of 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which is a precursor of leukotrienes A_4(LTA_4) (ref. 23). In mast cells and also in monocyte/macrophages, LTA_4 is conjugated with glutathione to give rise to leukotriene C_4(LTC_4) which may be converted into LTD_4—a molecule in which the glutamine residue is lost from glutathione and then to LTE_4 (Figure 1). Degranulation of mast cells with release of LTC_4 and LTD_4 and other mediators of immediate hypersensitivity is thought to trigger the bronchospasm and mucosal oedema in bronchial asthma[24]. Acetyl glycerol ether phosphorylcholine, also called as platelet-activating factor (Figure 2), is another potent lipid inflammatory mediator[25]. It induces chemotaxis, aggregation, degranulation and respiratory burst in neutrophils.

Glucocorticoids protect against the release of these mediators such as histamine, serotonin, degradative enzymes, etc. by checking the degranulation[26]. It has been suggested that glucocorticoids inhibit histamine synthesis and stabilize lysosomal membrane against degranulation. Increased level of cortisol, a principal glucocorticoid in man, may help to prevent autoimmune response to tissue antigen. In human, glucocorticoids have been shown to affect every step in both immunological and inflammatory actions by inhibiting the (i) production and activity of vasoactive agents, (ii) the movement of leukocytes to the inflamed area, and (iii) the function of immunocompetent cells at the site of inflammation.

Glucocorticoids decrease markedly the number of polymorphonuclear leukocytes, monocyte/macrophages and lymphocytes that accumulate. The actions may be due in part to the fact that glucocorticoids can inhibit chemotactic and other factors such as plasminogen activator that affects anti-inflammatory cell accumulation at the site of injury and may be a major mechanism for anti-inflammatory actions of glucocorticoids[28].

Therapeutic significance

The glucocorticoids have a significant therapeutic role in the field of medicine. In dozens of disorders, they find application, e.g. rheumatoid arthritis, bronchial asthma, ulcerative colitis, allergic rhinitis, etc. In adult human beings, the adrenal glands produce 20–35 mg of cortisol per day which is too meagre to cause any physiological effect and hence supraphysiologic doses of glucocorticoids are required to produce anti-inflammatory effects. This need led to synthesis of certain powerful

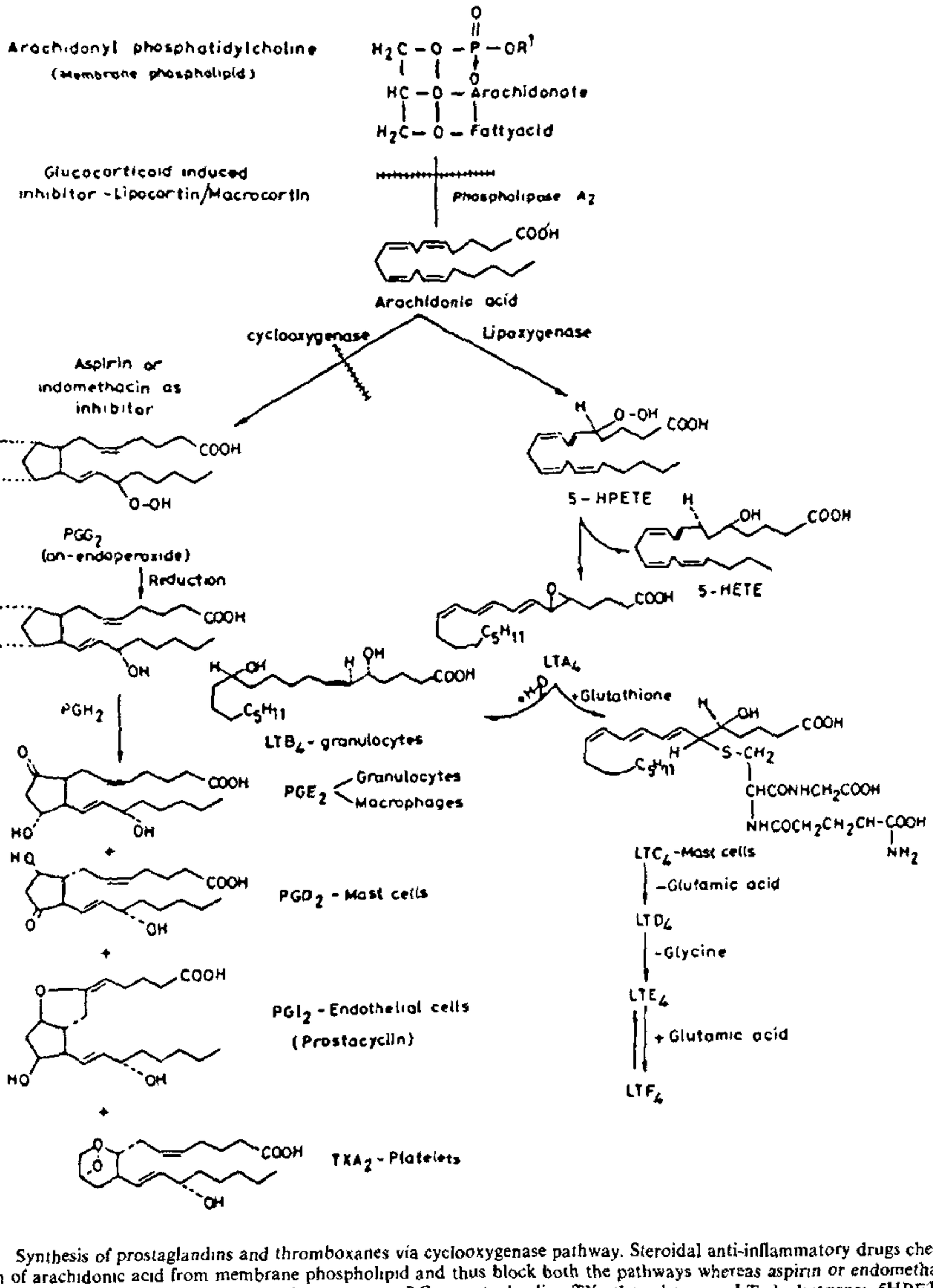

Figure 1. Synthesis of prostaglandins and thromboxanes via cyclooxygenase pathway. Steroidal anti-inflammatory drugs check the formation of arachidonic acid from membrane phospholipid and thus block both the pathways whereas aspirin or endomethacin, a non-steroidal drug, leaves lipoxygenase pathway intact. PG, prostaglandin; TX, thromboxane; LT, leukotriene; 5HPETE, 5-hydroperoxyeicosatetraenoic acid; 5HETE, 5-hydroxyeicosatetraenoic acid.

anti-inflammatory corticoids for therapy. Dexamethasone is 30 times more powerful than cortisol—a natural corticoid. Some of the very common therapeutic corticoids, prescribed generally in medical practice, are listed in Table 1.

Structural and functional aspects

All the glucocorticoids have a 1, 2-cyclopentenoperhydrophenanthrene nucleus consisting of 4 rings (Figure 3). The 4–5 double bond and 3-ketone are essential for

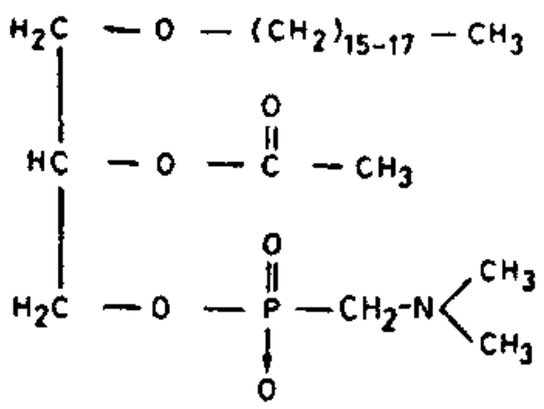

Figure 2. Platelet activating factor.

Table 1. Relative anti-inflammatory (AI) potencies of various therapeutic glucocorticoids

Compound	AI potency
Hydrocortisone (cortisol)	1
Cortisone	0.8
Prednisone acetate (Δ^1-cortisol)	3.5
Prednisolone acetate	4
Triamcinolone (9-α-Fluoro-16α hydroxyprednisolone)	5
6-α-Methyl prednisolone	5
Paramethasone (6α-Fluoro-16α-methylprednisolone)	10
9-α-Fluorohydrocortisone	15
Betamethasone (9α-Fluoro-16β-methylprednisolone)	25
Dexamethasone (9α-Fluoro-16α-methylprednisolone)	30

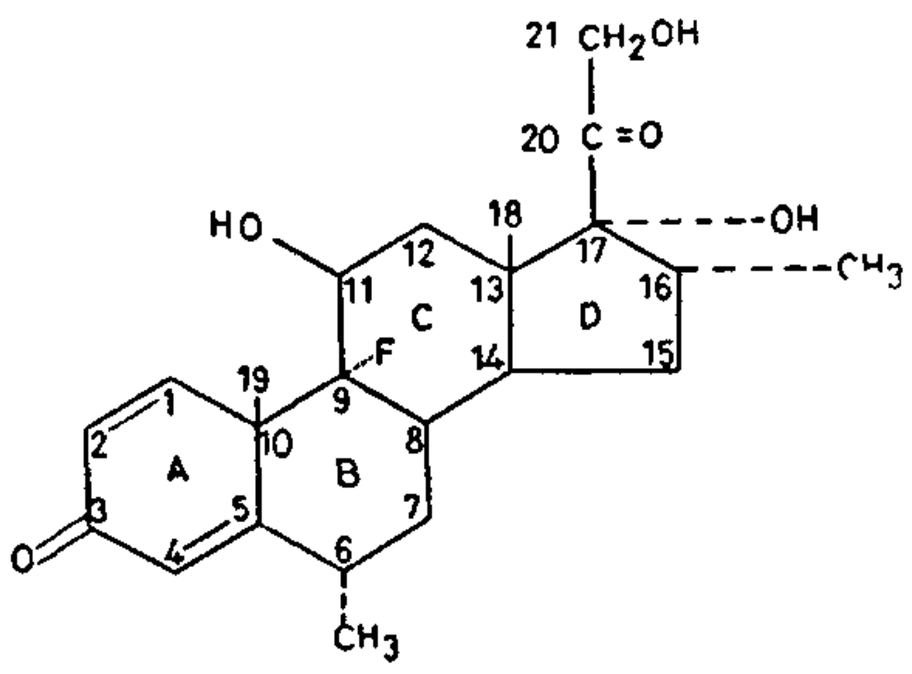

Figure 3. Structure of glucocorticoids, heavier lines indicate the common structure to all corticoids.

typical adrenocorticosteroid activity[28]. Introduction of 1–2 double bond in prednisone increases the carbohydrate-regulating property of corticoids. The biological activities of steroids are remarkably enhanced by 9-fluorination in ring B (ref. 29). The presence of an oxygen function at C-11, in ring C is a must for anti-inflammatory as well as carbohydrate regulatory properties of corticosteroids. All available anti-inflammatory corticoids are 17-hydroxy compounds[30]. Natural and many other synthetic corticoids have a 21-hydroxy group. Though all the glucocorticoids mentioned in the Table 1 have wide therapeutic application, no glucocorticoid is unique in being therapeutic without eliciting some harmful effects.

Conclusion

The mechanism of anti-inflammatory actions of glucocorticoid is complex. Glucocorticoids tend to suppress entire inflammatory processes and therefore the products of everything characteristic of it—capillary permeability, diapedesis, exudate, antibody formation, granulomatous proliferation and repair process. Despite there being considerable knowledge of glucocorticoid action at the cellular and metabolic levels, an integrated understanding of their anti-inflammatory effects is still lacking.

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REVIEW ARTICLE

Nitrogenous pollutants in the atmosphere: Their assimilation and phytotoxicity

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Most plants possess well-characterized physiological and biochemical systems to absorb nitrogenous gases from the atmosphere and to assimilate the nitrogen into organic nitrogenous compounds. The system is often activated during the exposure of plants to low level of the gases with concurrent increases in organic nitrogen content and growth of the plants. The nitrogenous gases, however, are not the complete replacement of soil nitrogen or other usual modes of nitrogen nutrition and often the exposure to these gases at relatively higher concentrations results in some physiological and morphological aberrations in plants. Apparently, there are some unknown constraints on the optimum utilization of nitrogenous gases as sources of nutrient nitrogen, which are perhaps linked to their phytotoxic reactions.

NITROGENOUS gases from natural as well as anthropogenic sources are important contributors to the atmospheric pollution. Total annual emission of these gases has been estimated to be about 64×10^8 tons from natural sources and about 57×10^6 tons from man-made sources[1]. Nitric oxide, NO_2, N_2O and NH_3 are the principal components of these pollutants, although trace amounts of other nitrogenous compounds such as N_2O_5, HNO_3 vapours, nitrogenous amines and volatile hydrocarbons are also present in the atmosphere. Nitrogen oxides (NO_x) are formed by the heat-promoted combination of atmospheric nitrogen and oxygen. Oxidation of nitrogenous compounds in fuel and biological materials and microbial conversion of excess nitrogen fertilizers in the soil also contribute towards NO_x production.

The phytotoxicity of nitrogenous air pollutants is well established[2–4]. Considering that nitrogen is the most abundant (constituting about 1 to 5% of a plant's dry weight) mineral element in plants and that most of the nitrogenous pollutants are assimilable compounds, these phytotoxic effects are rather inconceivable. But, careful studies with low levels of many pollutants have shown that the pollutants do increase plant growth in some cases[4,5]. The growth of plants in the presence of either NO or NO_2 as a sole source of nutrient nitrogen, however, is not comparable to that with soil nitrate as nutrient nitrogen[4,6,7]. Clearly, there are some constraints on the optimum utilization of NO/NO_2 and perhaps other nitrogenous gases as well, as a source of nutrient nitrogen. The knowledge of the physiological and biochemical basis of phytotoxicity may help in understanding the possible constraints in the role of nitrogenous air pollutants as alternate sources of nitrogen.

Ammonia

In temperate zone toposphere, the concentration of ammonia has been recorded to be around 10 ppb (ref. 8),