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AUTOIMMUNITY INDUCED BY CHEMICALS

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ABSTRACT

Immunotoxicologic studies have demonstrated that autoimmune responses and/or autoimmune diseases are induced in humans and experimental animals by chronic exposure to various chemicals. The present review is focused on seven groups of chemically induced human disorders, i.e. systemic lupus erythematosus, autoimmune hemolytic anemia, myasthenia gravis, pemphigus, glomerulonephritis, thyroiditis and hepatitis. Results obtained from studies of the available experimental counterparts of these diseases, i.e. those models obtained from the exposure of laboratory animals to various chemicals, are then analyzed. Finally, we present the lessons that can be derived from immunotoxicologic investigations regarding mechanisms of induction, heterogeneity of chemicals involved, humoral vs. cellular immune responses and genetic predisposition to chemically induced autoimmunity.

INTRODUCTION

It has long been recognized that certain drugs are capable of inducing autoimmune responses and, less frequently, autoimmune disease. The first report of such an occurrence goes back to 1945, when Hoffman described a patient with a clinical syndrome compatible with the diagnosis of sytemic lupus erythematosus that coincided with the administration of sulfadiazine.

different specificities) are induced by both procainamide and hydralazine. A genetically controlled polymorphism of the hepatic acetyltransferase enzymes regulates the rate of inactivation of hydralazine and individuals may be distinguished as slow or rapid acetylators. Slow acetylators are more prone to develop antinuclear antibodies and DRL following the administration of hydralazine and similar drugs. This phenomenon is of interest since aromatic amines or hydrazine compounds are present in our food supply and in the environment. Hydrazines are found in mushrooms, tobacco and tobacco smoke. Aromatic amines are used in hair coloring solutions. Human disease caused by hydrazine or by the ingestion of alfalfa seeds, containing a primary amine, 1-canavanine, has been reported (13). In addition to acetylator phenotype, other factors, such as the association with HLA-DR4 phenotype and/or the C4 null allele, may predispose to the development of hydralazine-induced SLE (15).

b. Lupus Induced by Penicillamine and Other Drugs.

Penicillamine is a drug used as a chelating agent to remove excess copper in patients with Wilson's disease, to reduce excess cystine excretion in cystinuria and also administered to patients with active rheumatoid arthritis who have failed to respond to conventional therapy. It can induce a variety of autoimmune syndromes, such as myasthenia gravis and pemphigus (see below). Perhaps less investigated is the induction of antinuclear antibodies and DRL (16,17). This was first reported in 1968 in a patient with Wilson's disease, suggesting that patients do not require a predisposition to an autoimmune disorder to develop DRL. Penicillamine can induce lupus in as many as 2% of patients, with clinical presentation ranging from an asymptomatic serologic disease to a severe illness with widespread joint pain, synovitis, rash, malaise, weight loss, nephritis, pleurisy and neurologic disturbances. ANA, anti-DNA antibodies and a lupus band test (deposition of immunoglobulins and complement along the dermal-epidermal junction of the skin) have been reported in these patients, a striking difference versus the DRL induced by hydralazine and other drugs. Recently, a controlled study has found no difference in the frequency of ANA in patients with rheumatoid arthritis treated with D-penicillamine versus those treated with [illegible] (18). On the other hand, in vitro experiments using peripheral blood

mononuclear cells from SLE patients and controls have demonstrated that D-penicillamine can act as an immunomodulator capable of potentiating and initiating anti-DNA antibody synthesis as well as suppressing it (19). In view of the other autoimmune effects of this drug, it seems obvious that additional studies, both experimental and clinical, should be performed to ascertain the lupus-inducing potential of penicillamine and related chemicals. Finally, it should be noted that circulating ANA and immune complexes have been detected in workers exposed to vinyl chloride, asbestos and silica (20,21) and that a variety of disorders, including SLE, has been reported to follow the injection or implantation of paraffin/silicone and silicone polymers for cosmetic reasons (22).

2. Autoimmune Hemolytic Anemia and Thrombocytopenia

In 1966 it was first noted that a high proportion of patients taking methyldopa developed a positive direct antiglobulin test and that some of them had hemolytic anemia. The antibody responsible was IgG and the free serum antibody and the eluate from the red cells reacted with normal red cells in the absence of the drug. The antibody may have specificity for the Rh blood group system: in many patients a number of different antibodies are found, some with anti-c and anti-e specificity and others that react with all cells including Rh-null cells (23). The antibody develops after several weeks of exposure to methyldopa and the titer and incidence of positive tests are dose-dependent. When the drug is withdrawn the direct antiglobulin test remains positive for weeks or months before gradually becoming negative. Reintroduction of the drug leads to reappearance of the antibody, again with a similar lag period. Red cell autoantibodies develop in approximately 20% of patients receiving methyldopa, yet hemolysis occurs less frequently. This may be due to a drug-induced impairment of reticuloendothelial function (24). Autoantibodies to red cells and autoimmune hemolytic anemia have also been reported in patients receiving procainamide or chlorpropamide (25,26). Anti-platelet antibodies and autoimmune thrombocytopenia have been observed in patients treated with carbamazepine or undergoing gold therapy (27,28). Finally, a case of autoimmune thrombocytopenia related to interferon therapy has been recently reported (29).

3. Myasthenia Gravis

A clinical syndrome apparently identical to myasthenia gravis (MG) may follow penicillamine treatment of patients with rheumatoid arthritis, Wilson's disease and cystinuria (7,16,17,30). The two latter conditions are not of an immunologic nature and are not usually associated with myasthenia gravis, which underlines the etiologic role of the drug. In general, MG is induced by long-term penicillamine treatment, i.e. after many months to years, and the syndrome usually improves after withdrawal of the drug. Autoantibodies to acetylcholine (Ach) receptors are found in sera of patients with penicillamine-induced MG and their titers decrease gradually after the drug is withdrawn. Both the clinical syndrome and autoantibodies to Ach receptors are found in 0.5% of subjects treated with penicillamine.

A recent study (7) of immuno-clinical correlations in 23 cases of D-penicillamine-induced MG has confirmed that from a clinical point of view there seems to be no major difference between idiopathic and drug-induced disease, even though the latter is usually less severe and presents more frequently with ocular manifestations (ptosis or diplopia). Serologically, antibodies to Ach receptors were detected in 83% of cases, but there was not a good correlation between antibody titers and severity of MG or dosages of D-penicillamine. Interestingly, 5 cases had persistent MG (for a period of 24 months or longer) in spite of the interruption of penicillamine treatment. As usual, one wonders whether such patients would have developed MG independently of their exposure to penicillamine. On the other hand, they might also be an example of irreversible autoimmune disease induced by chemicals.

4. Pemphigus

Skin lesions similar to pemphigus blisters develop in patients receiving penicillamine and have been diagnosed as pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus and bullous pemphigoid (16,17,30,31). Skin biopsies show typical findings of pemphigus or pemphigoid, with deposition of immunoglobulins at the intercellular level or at the basement membrane level. Approximately 70% of the cases of pemphigus have circulating

autoantibodies to the intercellular substance of the skin, whereas circulating autoantibodies to the basement zone are detected in penicillamine-induced bullous pemphigoid. In general, termination of treatment is followed by a decrease in autoantibody titers and clinical improvement. Similarly, pemphigus has been observed in patients treated with other sulfhydryl compounds (pyrithioxine, alpha-mercaptopropionylglycine, captopril) (32).

5. Glomerulonephritis

Evidence for renal injury caused by drugs through immunologic mechanisms has been accumulating in the past 30 years (33,34) whereas less attention has been given to the biologic effects of environmental toxins and pollutants. However, it is now agreed that a variety of chemicals can induce kidney disease in humans by the formation of immune complexes, possibly composed of autoantigens and autoantibodies, or the induction of autoantibodies to renal antigens (35-37).

a. Mediated by Immune Complexes.

Immune complex-mediated renal disease is a very rare manifestation of drug related lupus (see above). However, renal lupus syndromes following penicillamine treatment have been reported (38). In addition, proteinuria has been observed in 7 to 20% of penicillamine-treated patients with rheumatoid arthritis, whose renal biopsies showed evidence of membranous nephropathy, with finely granular deposits of IgG and complement along the capillary walls (16,17,30). IgM nephropathy may also be associated with penicillamine (39).

Chronic mercury intoxication may similarly result in membranous nephropathy, possibly with an autoimmune pathogenesis, induced in predisposed subjects by exposure to the chemical. This hypothesis is supported by the observation that kidney biopsies from these patients contain deposits of immunoglobulins and complement at the level of the glomerular basement membrane (40). There are no data indicating that the metal itself or one of its metabolites is the antigen responsible for immune complex formation and

the consistent lack of mercury in the immune deposits argues against this possibility (35). The mechanism(s) of the autoimmune effects of mercury are still unknown, but this metal has been shown to affect the functions of lymphocytes (4), polymorphonuclear leukocytes (41) and macrophages (Contrino et al., in preparation).

Other metals are capable of inducing immune complex-mediated glomerulonephritis, possibly on an autoimmune basis. It has been suggested that cadmium may have such property (42) and numerous reports are available on similar effects of gold (43). Mild proteinuria is observed in about 10% of patients with rheumatoid arthritis treated with gold salts, while massive proteinuria is observed in 1%. Diffuse granular deposits of immunoglobulins and complement are detected in the glomeruli, but gold is not found at this level (44,45). Therefore, it is unlikely that the immunoglobulin deposits contain gold-binding proteins or are part of hapten-antibody complexes. Interestingly, the relative risk of proteinuria during gold treatment of rheumatoid arthritis is increased 32 times in patients who are HLA-DRw3 positive (46). The relationship between certain HLA haplotypes and the development of nephropathy during gold therapy has been recently confirmed (15). These observations suggest the involvement of immune response genes in autoimmune manifestations induced by gold and perhaps other chemicals.

b. Mediated by Autoantibodies to Renal Antigens.

Penicillamine has been reported as the cause of Goodpasture's syndrome in a few patients with rheumatoid arthritis or Wilson's disease, but anti-glomerular basement membrane antibodies have not been detected in the drug-induced disease (16). Similarly, hydrocarbon solvent exposure has been suggested as a mechanism for the development of Goodpasture's syndrome, but as yet there is no solid evidence in favor of this hypothesis (47). On the other hand, antibodies against the renal glomerular basement membrane have been detected in the circulation of patients during the Spanish epidemic of poisoning from ingestion of rapeseed oil adulterated with aniline (48).

6. Autoimmune Thyroid Disease

The environmental factors that may play a role in the pathogenesis and progression of autoimmune thyroid disease (Hashimoto's disease, Graves' disease) have been recently reviewed (49). Increasing evidence suggests that dietary iodine is an important factor in the development of these disorders. In addition, various environmental pollutants, such as polybromated biphenyls (PBB) and polychlorinated biphenyls (PCB) have been implicated in the induction of autoimmune thyroid disease (49).

Treatment of manic-depressive patients with lithium may induce the formation of thyroid autoantibodies (against thyroglobulin and/or microsomal antigen) and thyroid dysfunction (both subclinical and overt hypothyroidism) (50-52). However, thyroid autoantibodies are not detected in all patients rendered hypothyroid by this treatment (53). It has also been observed that the functional effects of lithium are apparently not associated with the presence of thyrotropin-binding immunoglobulins (54). Autoimmune thyroiditis has also been associated with anticonvulsant therapy (55) and penicillamine treatment (16). Antibodies to thyroglobulin and thyroid microsomal antigen as well as low titer thyroid-stimulating immunoglobulins are frequently found in patients receiving amiodarone, an iodinated benzofuran derivative utilized as an antiarrhythmic and anti-anginal drug (56,57). In one series, two patients had clinical abnormalities associated with Graves' disease, two patients were hypothyroid and the rest euthyroid. An analysis of peripheral blood lymphocytes revealed changes in T cell subsets, suggesting that amiodarone precipitates organ-specific autoimmunity of the thyroid in susceptible persons.

7. Hepatitis

Liver injury associated with the administration of certain drugs or exposure to environmental toxins is one of the major sources of hepatic disease, characterized by a variety of lesions comprising the whole spectrum of liver abnormalities produced by other agents (58,59). Because of this complexity, it is often difficult to determine a cause-effect relationship in

The influence of lithium on experimental autoimmune thyroiditis has been studied in female August rats (53). The levels of antibodies to thyroglobulin increased significantly in lithium-treated rats vs. controls in the period immediately after immunization with thyroglobulin. In contrast, animals that received lithium during the phase of spontaneous resolution of the disease showed a significant decrease in antibodies to thyroglobulin. Rats that received lithium but were not immunized did not have circulating antithyroglobulin antibodies. Lithium had no effect on the degree of lymphocytic infiltration of the thyroid in any of the treated groups. Finally, it has recently been reported that the intra-thyroid injection of murine recombinant interferon gamma induced the production of antibodies to thyroglobulin and thyroiditis in CBA mice (102).

THE LESSONS OF CHEMICALLY INDUCED AUTOIMMUNITY

A notable increase in autoimmune disease has been observed in several countries. In part, this phenomenon is due to more sophisticated diagnostic procedures and enhanced physicians' awareness of autoimmunity. However, it may also be due to a rising attack rate. As an example, a true increase in the incidence of Hashimoto's thyroiditis was noted at the Mayo Clinic (103). Similarly, a higher incidence of systemic lupus erythematosus has been observed in urban areas and is presumed to represent an environmental factor as yet undefined, in addition to any genetic predisposition that might exist (104). From this point of view, several lessons can be derived from the study of autoimmunity induced by chemicals.

First, autoimmune responses and disease may result from exposure to drugs and other compounds through a variety of mechanisms (see Table 1). Chemicals may combine with autoantigens and modify them, so that they are no longer recognized as "self". This may occur through conformational changes, providing new antigenic determinants or exposing hidden ones, as may happen after chronic treatment with hydralazine (that is known to form complexes with deoxyribonucleoprotein) or procainamide (that binds to photo-oxidized single- and double-stranded DNA). Penicillamine may also modify autoantigens due to the presence of the highly reactive thiol group.

TABLE 1

INDUCTION OF AUTOIMMUNITY BY CHEMICALS

SUGGESTED MECHANISMS	CHEMICALS(*)
COMPLEX WITH AUTOANTIGEN	Hydralazine (105)
RELEASE OF AUTOANTIGEN	Gold (90), Cadmium (42)
CROSS-REACTION WITH AUTOANTIGEN	Hydralazine (106)
IMMUNOGEN OR HAPTEN	Penicillamine (107)
INHIBITION OF T SUPPRESSOR CELLS	Methyldopa (108), Practolol and Procainamide (109, 110), Mercury (74)
STIMULATION OF T HELPER CELLS	Procainamide (111), Beta blockers and Phenytoin (112), Mercury (36)
STIMULATION OF B CELLS	Mercury (36), Beta blockers and Phenytoin (112), Penicillamine (16), Iodine (49)
STIMULATION OF MACROPHAGES	Penicillamine and Propylthiouracyl (71), Iodine (49)
CHANGES IN PRODUCTION OF CYTOKINES AND LYMPHOKINES	?
ALTERED MHC EXPRESSION	?
ALTERATION OF IDIOTYPE-ANTI-IDIOTYPE NETWORK	?

(*)References in parentheses