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Iodine: an environmental trigger of thyroiditis☆

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Abstract

Like most autoimmune diseases of humans, chronic lymphocytic (Hashimoto's) thyroiditis results from the combination of a genetic predisposition and an environmental trigger. A body of clinical and epidemiologic evidence points to excessive ingestion of iodine as an environmental agent. In genetically determined thyroiditis in animals, iodine enrichment has been shown to increase the incidence and severity of disease. Its mechanism of action is still uncertain. Using a new animal model of autoimmune thyroiditis, the NOD.H2^{h4} mouse, we have been able to show that iodine enhances disease in a dose-dependent manner. Immunochemical studies suggest that iodine incorporation in the thyroglobulin may augment the antigenicity of this molecule by increasing the affinity of its determinants for the T-cell receptor or the MHC-presenting molecule either altering antigen processing or by affecting antigen presentation.

Keywords: Thyroiditis; Thyroglobulin; Iodine; Hashimoto's disease; NOD.H2^{h4}

Take-home messages

- Chronic lymphocytic thyroiditis (CLT) is a multifactorial autoimmune disease with genetic and environmental factors contributing to its development.
- The best-defined environmental factor is dietary iodine.
- Poorly-iodinated thyroglobulin is not well recognized by peripheral blood lymphocytes (PBL) from patients with CLT.
- Iodination of thyroglobulin promotes recognition and proliferation by patients' PBL.
- A new mouse model, NOD.H2^{h4}, develops autoimmune thyroiditis (AT) spontaneously in low prevalence. The disease closely resembles human thyroiditis.
- The prevalence and severity of AT in NOD.H2^{h4} mice are significantly increased by adding iodine to the drinking water.

Abbreviations: CLT: chronic lymphocytic thyroiditis; Tg: thyroglobulin ; TPO: thyroid peroxidase; MHC: major histocompatibility complex; RFLP: restriction fragment length polymorphism; PCR: polymerase chain reaction; HLA: human leukocyte antigen; TcR: T-cell receptor; T_3: triiodothyronine; T_4: thyronine; RDA: recommended daily allowance; AT: autoimmune thyroiditis; PBL: peripheral blood lymphocytes; APC: antigen-presenting cells; RT-PCR: reverse transcription-polymerase chain reaction

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1. Chronic lymphocytic thyroiditis

Autoimmune thyroid diseases encompass a number of thyroid disorders, varying clinically and histopathologically from the hypothyroidism of chronic lymphocytic thyroiditis (CLT) to the hyperthyroidism of Graves' disease. Chronic lymphocytic thyroiditis, a prototypic organ-specific autoimmune disorder was initially reported in 1912 by Hashimoto [1], who described the histopathological appearance of four goitrous patients. This condition, often referred to as Hashimoto's thyroiditis, is characterized by a diffuse mononuclear cell infiltration, reduced thyroid follicles, enlarged thyrocytes containing granular and pink cytoplasm, termed Hurthle cells, and circulating autoantibodies to two primary thyroid-specific antigens, thyroglobulin (Tg) and thyroid peroxidase (TPO). CLT is caused by a specific immune response to these thyroid antigens, culminating in thyroid inflammation, destruction and subsequent hypothyroidism [2]. Considerable effort has been devoted toward gaining a better understanding of this disorder, but the mechanism(s) responsible for initiating an autoimmune attack on the thyroid remain undetermined. Further insight into the immunologic and pathologic events that precede thyroid destruction in CLT undoubtedly would offer more effective treatments and avenues toward the prevention of CLT.

Like most human autoimmune diseases, CLT arises from a combination of genetic traits that heighten susceptibility in conjunction with some environmental trigger. In this brief article, we will review recent evidence pointing to iodine as an environmental trigger for CLT.

2. Genetic predisposition to Hashimoto's thyroiditis (HT)

Susceptibility to autoimmune disease is determined by the genetic constitution of the individual, including both major histocompatibility complex (MHC) and non-MHC genes. Yet possessing particular alleles for genes implicated as risk factors in autoimmune disease is not sufficient for the development of autoimmune disease in humans. Autoimmune disease is thought to occur in individuals having the appropriate genetic background who are exposed to an environmental trigger. Restriction fragment length polymorphism (RFLP) analyses, PCR techniques and HLA typing have revealed a polygenic predisposition to development of CLT. For example, one study has reported an increased frequency of HLA-DR4, DR5, DQw3.1, and DQA2 in CLT patients compared to normal controls [3]. Farid and colleagues reported that 80% of HT patients compared to 54% of normal individuals possessed the DRw52 allele [4]. One explanation for the association of particular HLA alleles and CLT is that autoantigenic peptides possess different binding affinities for different MHC alleles, but such a relationship has not been clearly defined. Potential non-MHC genes implicated in disease susceptibility includes co-stimulatory factors, regulatory cytokines, T-cell receptor (TcR) variable region genes and immunoglobulin genes [5].

3. Iodine and thyroid autoimmunity

Iodine is a necessary component of normal thyroid hormonogenesis. It is incorporated into tyrosine moieties of Tg as mono-iodotyrosine and di-iodotyrosine residues that subsequently undergo an oxidative coupling event leading to the formation of thyronine (T_4) and triiodothyronine (T_3) [6]. Exemplifying the absolute requirement for iodine consumption is cretinism, a congenic condition of severe physical and mental retardation resulting from extreme iodine deficiency [6].

Although the recommended daily allowance (RDA) of iodine for an adult is 150 μg/day, epidemiologic data suggest that many adults in North America may ingest as much as 500 μg/day upwards to 1 mg/day [7,8]. There appears to be a link between overconsumption of dietary iodine and the development of CLT [9]. Epidemiologic studies in humans have reported an increased prevalence of thyroiditis with the administration of supplementary dietary iodine [10–12]. A marked rise in lymphocytic infiltration and Tg and TPO autoantibodies has been observed in iodine-deficient geographical areas when iodine supplementation is introduced [11,12]. Further support for the role of iodine in inducing thyroiditis

comes from studies of patients receiving the iodine-rich drug, amiodarone, an anti-arrhythmic, which demonstrate significant increases in Tg autoantibodies [13]. Furthermore, the epidemiologic data associating iodine intake with thyroiditis are supplemented by animal models where dietary iodine ingestion increased the incidence and severity of autoimmune thyroiditis (AT) in genetically susceptible BB/B rats [14], hamsters [15], and NOD.H2^{h4} mice [16].

The role of iodine in the pathogenesis of AT was described in experimental studies of T-cell responses to Tg. Several lines of evidence strongly suggest that iodination of Tg is critical for the recognition by Tg-reactive T cells [17,18]. Champion et al. [17] first reported that murine-derived Tg-specific T-cell lines only recognize and proliferate to human Tg if it was adequately iodinated, while the same cells did not respond to poorly iodinated Tg. In addition, iodine-depleted Tg failed to induce significant thyroid lesions compared to normal mouse Tg, suggesting once again the importance of sufficiently iodinated Tg in the activation of Tg-reactive T cells. More recent evidence has demonstrated the importance of iodination in the recognition of thyroglobulin by human T cells. Rasooly et al. showed that peripheral blood lymphocytes (PBL) from CLT patients and normal controls proliferated in response to normal Tg and highly iodinated Tg, while not responding to non-toxic goiter Tg that lacks iodine [19]. The proliferative response of patient and normal control lymphocytes to Tg was restored when non-toxic goiter Tg was iodinated in vitro, thus providing direct evidence for the critical role of iodination in Tg antigenicity. Additional support for the importance of iodine in immune recognition has come from antibody competition assays where Saboori et al. demonstrated that murine anti-human Tg monoclonal antibody recognition of Tg was dependent on the position and content of iodine [20].

4. Enhanced Tg autoantigenicity

While the evidence demonstrating that the iodination of Tg promotes Tg-reactive lymphocyte recognition and proliferation is compelling, the mechanism(s) by which iodine enhances the autoantigenicity of Tg remains unknown. In vitro evidence suggests that iodine may directly affect macrophages, dendritic cells, B cells and T cells [14]. These effects include stimulating macrophage myeloperoxidase activity, augmenting the maturation of dendritic cells, increasing the number of circulating T cells and stimulating B-cell immunoglobulin production. Iodine might also enhance the uptake, processing and presentation of Tg by professional antigen-presenting cells (APC), such as dendritic cells, macrophages and B cells. If activation of autoreactive Tg-specific T cells is important in the autoimmune response, iodine may promote their activation by increasing the affinity of critical peptides to MHC class II molecules. Iodine may increase the affinity of the TcR for the MHC class II peptide complex to a threshold level sufficient for T-cell activation [21]. Finally, high doses of iodine were shown to be toxic to human thyrocytes in vitro, possibly through oxygen radical attack [22]. If this were to occur in vivo, target autoantigens may be liberated from the thyrocytes and presented in sufficient levels to activate autoreactive T cells [5].

5. NOD.H2^{h4} Mouse — a model for human autoimmune thyroiditis

To investigate the role of dietary iodine in the induction and pathogenesis of AT, current studies in our laboratory focus on a new animal model for human AT, the NOD.H2^{h4} mouse. This mouse was produced by backcrossing the NOD.H2^{g7} strain, which spontaneously develops diabetes and a low incidence of thyroiditis, with B10.A(4R)-H2^{h4} strain, selecting for K$^{d/k}$ after each filial generation (Linda Wicker, personal communication). The result of this genetic backcross is the selection of the K haplotype at the MHC class II locus, I-A^{k}, from the B10.A(4R) strain, on the NOD background. Mice with the H-2^{k} haplotype are good responders to Tg [23]. Consequently, the NOD.H2^{h4} mouse is not susceptible to diabetes and shows a greater incidence of thyroiditis. Furthermore, administration of 0.05% NaI for 8 weeks, to the drinking water of these mice, significantly increases the incidence of thyroiditis [19].

Iodine supplementation also increases the levels of total Tg-specific antibodies and Tg-specific IgG2b compared to non-fed controls. In fact, serum titers of IgG2b correlated significantly with the presence of thyroid lesions. Splenocytes from NOD.H2^{h4} mice not fed iodine demonstrated a significant increase in proliferation to murine Tg compared to non-NOD strains, while the proliferation of splenocytes from iodine-fed NOD.H2^{h4} mice increased two-fold compared to non-fed mice. These findings provide fresh insight into the interplay between genetic background and iodine as an environmental stimulus in determining the onset of thyroiditis. For example, TGF-β may play a role in susceptibility because the presence of IgG2b correlated with thyroid lesions.

6. Mechanisms of action of iodine

Iodine may promote AT in NOD.H2^{h4} in a number of ways. First, iodine may affect the Tg molecule directly, creating new epitopes or exposing 'cryptic' epitopes. Second, the highly iodinated Tg molecule may facilitate antigen uptake and processing by APCs. Third, presentation of certain iodinated peptides within the MHC class II on the APCs may have a higher binding affinity for TcRs of T-helper cells. B cells, particularly, may be involved with antigen presentation of highly iodinated peptides, since we have determined that certain antibodies bind more strongly to highly iodinated Tgs than to iodine-free Tg [20,24]. Fourth, T-cell help, in turn, may divert the immune response from a benign response to a pathogenic one via cytokine responses, (e.g. vs. Th2).

Other investigators demonstrated that both CD4 and CD8 cells are required for the initiation of AT in the iodine-enhanced AT NOD.H2^{h4} model [25,26]. However, only CD4 cells are required to maintain chronicity of the disease, since depletion, after disease developed, of CD4 cells but not of CD8 cells reduced disease severity [25]. This suggests that CD8 cells are not necessary for maintaining progression into thyroiditis. Braley-Mullen et al. further demonstrated that B cells, especially early in life, were required for the initiation of disease in NOD.H2^{h4} mice [27]. These investigators depleted B cells with an anti-IgM treatment and found that thyroiditis was severely compromised [27]. Passive transfer of antibody or reconstitution of adults with B cells did not induce AT [27], suggesting further that there was early requirement for B cells and that B cells are important in a role other than antibody production. The most likely role is that of antigen presentation; the role of B cells as antigen-presenting cells needs to be further investigated.

These results also suggest that the required events for the initiation and the chronic stage of disease are different. Evidence from our laboratory and others show virtually no reduction of established disease after excess iodine was stopped [25,26]. This suggests that once disease is triggered, the inciting agent is no longer necessary. Therefore, the initial events are of special importance in this disease.

Initial events include (i) the presentation of antigen by APCs and (ii) recognition by T cells and response to the relevant antigen. The microenvironment within which the APC develops and presents antigen to the T cell influences the T-cell response. There is increasing evidence that the microenvironment has profound effects on APCs and subsets of APCs [28] which, in turn, influences the class of T-cell development. The different subsets of APCs (macrophages, dendritic cells, B cells) secrete different cytokine mixtures, thereby influencing the T-cell development [28]. Furthermore, there appear to be endogenous compounds, such as components of cell surfaces and extracellular matrices that preferentially stimulate the APCs directly [29,30]. These findings are important because they might suggest that perturbation of the thyroid, perhaps by excess iodine [22,31] affects APCs. The APCs can alter the microenvironment; the microenvironment, in turn, affects the development of T cells.

There is little understanding of whether poorly or highly iodinated Tg affects APCs directly. Early work by Weetman et al. [32] showed that iodide enhanced IgG synthesis by human PBLs in vitro. Mooij et al. [33] showed that differentially iodinated thyroid hormones and Tg enhanced the differentiation of human monocytes into dendritic cells. Non-iodinated Tg showed less of a response [33]. To sum up, iodine can affect B cells and

iodinated molecules of the thyroid gland can affect the transition of monocytes into dendritic cells. Thus it is possible that iodine acts by altering APCs directly to initiate the events that lead to thyroiditis.

In theory, polarization of the T-cell response depends on the microenvironment of cytokines: IL-12 generally favors the Th1 response, whereas IL-4 directs a Th2 response. The polarity thus created may determine the disease outcome. However, in both human AT and our NOD.H2^{h4} model of AT, virtually all cytokines of the Th1 and Th2 pathways have been found. For example, Ajjan et al. [34] studied the mRNA cytokine profiles in tissue from CLT patients, using reverse transcription-polymerase (RT-PCR). They found IL-1b, IL-1a, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ (and TNF-α). Other investigators [35] showed similar findings of both Th1 and Th2 cytokine messages in intrathyroidal lymphocytes in human thyroiditis or Graves' patient tissue. In the NOD.H2^{h4} mouse model, Braley-Mullen et al. found up-regulated mRNA expression of IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IFN-γ and TNF-α in the thyroid after 2–4 weeks of iodine supplementation [25]. Furthermore, thyroids and spleens were found to have increased markers of cytokines, macrophages, T-cell and B-cell activation within 2–4 weeks of iodine treatment [36]. A report of increased cytokine expression by mRNA message levels in the BB/W rat indicated that, again, Th1 and Th2 cytokines are found in the thyroid gland [37]. However, this group segregated those animals with and without disease, and found that those animals with thyroiditis were more likely to express early Th1 cytokines, especially IL-12 [37]. One limitation to all the studies utilizing the PCR technique is that it is not possible to distinguish which cell or tissue is producing the mRNA. Furthermore, gene expression is not always equivalent to protein expression.

Previous work in our laboratory indicated that IL-12 and IFN-γ are critical in the pathophysiology of experimentally induced thyroiditis in the mouse [38,39]. Immunohistochemical studies on the iodine-enhanced thyroiditis NOD.H2^{h4} model showed that scattered cells secreting IL-12 and IFN-γ were found early in disease, before focal accumulations of cells were present. These findings suggest that, soon after iodine supplementation, the cell responses may be skewed toward a Th1 response.

T-cell lines/clones will further our understanding of what is happening to the cells when the T cell is presented with highly iodinated Tg compared to poorly iodinated Tg. We have already developed cloned lines from NOD.H2^{h4} mice that received excess dietary iodine in their drinking water. The six cloned lines all bear the CD4 phenotype. However, they also bear markers of NK cells. TcR analysis showed that the NKT-associated TcR rearrangement of Vα14-Jα281 in all six lines. Each cloned cell line is unique in its proliferative response to mouse Tg with high or low iodine content. At least one cloned line, 2D11, discriminates strikingly between the two Tg preparations with only minimal proliferative responses to poorly-defined Tg, but a vigorous response to highly-iodinated Tg. The individual cell lines also differ in their cytokine profiles when stimulated by Tg. Preliminary evidence shows that some lines function to enhance disease and antibody production in young NOD.H2^{h4} recipients given these cells by adoptive transfer.

7. Similarity to human disease

Several lines of evidence suggest that the NOD.H2^{h4} mouse is a good animal model for human CLT. Firstly, the administration of iodine to genetically susceptible mice increases the incidence of thyroiditis in our model, which supports epidemiologic data on human populations. Secondly, the presence of high levels of IgG2b in iodine-fed NOD.H2^{h4} mice is similar to humans in that the predominate IgG subclass in CLT patients is IgG2, the human analog of murine IgG2b [40]. Thirdly, both CLT patients and NOD.H2^{h4} mice demonstrate differences in the isotypes of Tg-reactive antibodies when compared to normal controls. Tg-reactive antibodies of normal individuals and mice are generally IgM, whereas CLT patients and diseased mice predominantly produce Tg autoantibodies of the IgG isotype. Fourthly, a diffuse mononuclear cell infiltration is common to both CLT patients and NOD.H2^{h4} mice.

However, differences exist between our mouse model of iodine-induced AT and HT. Firstly, in the NOD.H2^{h4} mouse model, female mice do not exhibit a greater prevalence of disease, which is in stark contrast to human data. Secondly, anti-TPO antibodies are absent in NOD.H2^{h4} mice, while generally diagnostic of HT.

There is powerful evidence that the environmental agents play a critical role in triggering autoimmune disease in genetically susceptible hosts. There is, however, little information about how such agents work. By using a well-defined mouse model, the NOD.H2^{h4} mouse, and a well-documented environmental trigger, iodine, we can elucidate this fundamental issue.

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