Uptake and Metabolism of Iodine Is Crucial for the Development of Thyroiditis in Obese Strain Chickens

T. R. Brown,* R. S. Sundick,‡ A. Dhar, * D. Sheh,‡ and N. Bagchi
Department of Medicine, *Division of Endocrinology and Metabolism, ‡Immunology and Microbiology, Wayne State University, Detroit, Michigan 48201

Abstract
To assess the importance of the role of thyroidal iodine in the pathogenesis of thyroiditis in the obese strain (OS) chicken, a model of spontaneous and severe disease, we studied the effect of antithyroid drugs that reduce thyroidal iodine or prevent its metabolism. Reduction of thyroidal iodine was achieved with KC104, an inhibitor of iodine transport and mononitrotrosine (MNT), a drug that promotes loss of thyroidal iodine as iodotyroasine. A regimen consisting of KC104 and MNT administration beginning in ovo and continuing after hatching reduced thyroidal infiltration to 2% of control values and decreased thyroglobulin antibody (TgAb) production for as long as 9 wk. Untreated birds had severe disease by 5 wk of age. The suppression of disease was independent of TSH, not mediated by generalized immunosuppression and reversed by excess dietary iodine. Two drugs that inhibit the metabolism of iodine, propylthiouracil (PTU) and aminothiizolazole, reduced thyroidal infiltration and TgAb levels, although to a lesser extent. When splenocytes from OS chickens with thyroiditis were transferred to Cornell strain (CS) chickens, a related strain that develops late onset mild disease, only the recipients that were iodine supplemented developed thyroiditis. In conclusion, autoimmune thyroiditis in an animal model can be prevented by reducing thyroidal iodine or its metabolism and optimal effects require intervention at the embryonic stage. (J. Clin. Invest. 1991. 88:106-111.) Key words: autoimmune disease • antithyroid drugs • thyroid • immune suppression • etiology

Introduction
There is accumulating evidence which suggests that iodine, an environmental element that is an integral component of thyroid hormone and the prohormone thyroglobulin, plays an important role in the induction of autoimmune thyroiditis in cer-

1. Abbreviations used in this paper: CS, Cornell strain; MNT, mononitrotrosine; OS, obese strain; PTU, propylthiouracil; T4, thyroxine; Tg, thyroglobulin.

Received for publication 19 September 1990 and in revised form 11 January 1991.

1. Address correspondence to Thomas R. Brown, Ph.D., Wayne State University School of Medicine, 2125 Ellum Building, 421 East Canfield, Detroit, MI 48201.

were bled on day 1 at 37°C and overnight at 4°C. Separation was achieved by bringing the mixture to 2% with polyethylene glycol and centrifuging at 2,500g for 30 min. Values were expressed as the percentage of the total radioactivity that was specifically precipitated.

In later experiments an ELISA was used. Briefly, microtiter well plates (Dynatech, Chantilly, VA) were coated with high iodine Tg (10 μg/ml) and blocked with 2% BSA. The Tg was obtained from chickens that had been provided drinking water supplemented with KI (20 mg/dl) for 1 mo. Sera (100 μl of a 1:1,000 dilution) were incubated in the wells for 3 h at room temperature. The plates were then washed and phosphatase-labeled goat anti-chicken IgG (Kirkegaard and Perry, Gaithersburg, MD) was added. 1 h later the plates were washed and n-nitrophenylphosphate substrate (Kirkegaard and Perry) was added. Absorbance at 407 nm was determined using a microplate reader (Molecular Devices, Menlo Park, CA). Arbitrary units were assigned based on a calibration curve of dilutions of pooled OS sera previously determined to have high Tg antibody titers. A cutoff value of 8–12 units was set to minimize false negative and false positive values. The within assay CV at 1:1,000 serum dilutions was < 8%.

Thyroid histology. Paired thyroid lobes of each bird were fixed and embedded in paraffin. Multiple sections were cut and stained with hematoxylin and eosin. These sections were then examined by one of the authors (A. Dhari) who determined the percent of each cross-section of thyroid gland that was replaced by mononuclear leukocytes. The results for multiple sections, usually 10, were then averaged and this value was the percent infiltration for each chicken. When all of the slides were read the slide numbers were then decoded and grouped according to treatment protocol. The mean percent infiltration was then calculated by averaging the percent infiltration of all birds in that group.

Thyroidal distribution of radioiodine. To determine the optimal dose of propylthiouracil (PTU) and aminothiouracil, we determined their effect on thyroid iodine metabolism by examining the distribution of radioiodine in the thyroids of birds receiving these treatment regimens. Birds were injected i.p. with 125I (20 μCi/bird) and 20 h later their thyroids were weighed, homogenized in 0.05 M Tris-HCl, pH 7.5 containing 0.05 M methimazole and hydrolyzed with pronase (5 mg/ml) (Calbiochem-Behring Corp., San Diego, CA). The hydrolysates were analyzed by ascending paper chromatography using butanol:acetic acid (2 M) (1:1, vol/vol). The bands were detected by autoradiography and counted.

Tests of generalized immunosuppression. Chickens were given an i.p. injection of heat killed Brucella abortus (2.7 × 10^9 bacilli) kindly supplied by the National Veterinary Services Laboratory, Ames, IA) (Table IV, experiment 2). The animals were bled 10 d after the injection and the sera were tested for antibodies to Brucella abortus (10). Briefly, serially diluted sera (25 μl) were incubated with 25 μl of 1:100 diluted stock suspension of heat killed and stained Brucella abortus at 4°C overnight, and the wells were then read for agglutination.

In other experiments 3- or 4-wk-old birds were injected i.m. with 1 mg of bovine gamma globulin (BGG) in complete Freund’s adjuvant (Table IV). Antibodies to BGG were measured by ELISA according to the details described above for Tg antibody except that BGG was used to coat the plates and results were expressed in O.D. units.

Adoptive transfer. Recipient CS chicks homozygous for the major histocompatibility allele B11 obtained from Cornell University as fertile eggs were given 1 mg cyclophosphamide i.p. at hatching, 1 mg the next day and two injections of 1 mg each on the third day. At hatching half of these birds were placed on a high iodine regimen consisting of KI (20 mg/dl in the drinking water) and the other half were placed on a low iodine regimen consisting of KIO3 (0.1%) and MNT (10 mM in the drinking water). On the fourth day they were injected i.v. with 5 × 10^7 splenocytes in 0.2 ml culture medium isolated from 5-wk-old untreated OS donor chickens of the same major histocompatibility type. They were bled on day 10 and killed on day 23 at which time they were tested for TgAb and histology.

### Results

**Effect of iodine depletion on thyroid autoimmunity.** Iodine depletion was produced by treatment with KClO4 and MNT. KClO4 inhibits active iodine transport, whereas MNT, an inhibitor of iodotyrosine deiodinase, prevents recycling of thyroidal iodine and causes iodine depletion by promoting loss of iodine as iodotyrosines (11). A single injection of KClO4 and MNT at hatching followed by dietary KClO4 and MNT reduced thyroidal infiltration of 5-wk-old OS chickens to approximately half the value of the Tg-fed group (Table I). When this regimen was preceded by a single injection of KClO4 in ovo, infiltration was dramatically reduced. The most effective reduction of thyroid infiltration was achieved with 5 mg KClO4 in ovo. Subsequent experiments using in ovo KClO4 injections employed the 5-mg dosage.

**Effect of KClO4 in ovo on thyroidal iodine content at hatching.** A single injection of 5 mg KClO4 in ovo at 13 d of age caused a significant reduction in the thyroidal iodine content at hatching 7 d later from 443±54 to 86±17 μg/g±SEM (Student's t test, unpaired, P < 0.002). Thyroid weights were unchanged. The time of hatching was not delayed by this dose of KClO4 indicating that the embryos remained euthyroid.

**Effect of dietary combinations of KClO4, MNT, T4, and KI on autoimmune thyroiditis.** The effect of various combinations of dietary KClO4, MNT, T4, and KI in chickens treated in ovo and at hatching with KClO4, and MNT injections are shown in Table II. Dietary KClO4 without MNT did not have a significant effect on thyroidal infiltration or TgAb production. Dietary KClO4 + MNT significantly reduced thyroiditis when compared with birds receiving KClO4 alone. The addition of thyroxine to the diet suppressed TSH as indicated by lower thyroid gland weights but it did not alter the ability of KClO4 and MNT to prevent infiltration and antibody production. The addition of excess iodine to the KClO4 + MNT + T4 regimen increased infiltration toward control values thus providing evi-

---

**Table I. Effect of KClO4 Administered In Ovo on Thyroiditis in OS Chickens Examined at 5 wk of Age**

<table>
<thead>
<tr>
<th>Treatment of 13-d embryos</th>
<th>KCIO4 + MNT at hatching</th>
<th>Additions to diet</th>
<th>Thyroid infiltration mean (%±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>T4</td>
<td>None</td>
</tr>
<tr>
<td>None</td>
<td>+</td>
<td>T4, KClO4 + MNT</td>
<td>42±13</td>
</tr>
<tr>
<td>KClO4, 0.05 mg</td>
<td>+</td>
<td>T4, KClO4 + MNT</td>
<td>13±5</td>
</tr>
<tr>
<td>KClO4, 0.5 mg</td>
<td>+</td>
<td>T4, KClO4 + MNT</td>
<td>17±15</td>
</tr>
<tr>
<td>KClO4, 5 mg</td>
<td>+</td>
<td>T4, KClO4 + MNT</td>
<td>≥1</td>
</tr>
</tbody>
</table>

13-d embryos were given a single injection of KClO4. At hatching each chick received a single subcutaneous dose of 5 mg KClO4 to prevent thyroidal uptake of iodine and 11 mg MNT to prevent thyroidal reutilization of iodine. Thyroxine (20 μg/100 g), MNT (10 mM), and KClO4 (0.1%) were added to the diet for the duration of the experiment. There were six to eight birds per group and the data were analyzed by ANOVA + Fisher PLSD at P < 0.05 significance level. The infiltration in all experimental groups was significantly less than that of the T4 control. In addition, infiltration in the 5 mg KClO4 group was significantly less than the group receiving KClO4 + MNT at hatching.

**Iodine Is Crucial for Obese Strain Thyroiditis**
Table II. Effect of Combinations of Antithyroid Drugs, Thyroxine, and Excess Iodine on Thyroiditis in 5-wk-old OS Chickens

<table>
<thead>
<tr>
<th>Group number</th>
<th>KCIO₄ + MNT injections</th>
<th>Additions to diet</th>
<th>Thyroid weight</th>
<th>Thyroid infiltration (%)</th>
<th>TgAb (incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No T₄</td>
<td>ND</td>
<td>78±9</td>
<td>9/13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Yes None</td>
<td>48±2±12.0</td>
<td>88±2</td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Yes KCIO₄</td>
<td>67±2±17.9</td>
<td>70±14</td>
<td>7/10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Yes KCIO₄, MNT</td>
<td>13±4±11</td>
<td>2±1</td>
<td>2/7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Yes KCIO₄, MNT, T₄</td>
<td>3±1±3</td>
<td>6±2</td>
<td>0/7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Yes KCIO₄, MNT, T₄, KI</td>
<td>20±2±5</td>
<td>40±8</td>
<td>0/6</td>
<td></td>
</tr>
</tbody>
</table>

OS chickens were treated as above and killed at 5 wk. The values for thyroid weight and infiltration are mean±SEM of 6–13 chickens per group. TgAb was measured by ELISA. The details of treatment with KCIO₄, MNT, and T₄ are provided in Table I utilizing the 5 mg KCIO₄ protocol. KI (20 mg/dl) was added to the drinking water of group 6 for the duration of the experiment. Data were analyzed by ANOVA + Fisher PLSD at P < 0.05. Summary of infiltration: Groups 1, 2, and 3 do not differ from each other, but each differs from groups 4 and 5. Group 5 differs from group 6. Thyroid weight: Group 4 had the largest thyroids and the thyroids in groups 2 and 3 were larger than those in groups 5 and 6. TgAb incidence data was analyzed by multiple Chi-square analyses and subjected to a Bonferroni correction. Groups 4–6 had lower incidence of antibody than the control group 1 (P < 0.025). Groups 2 and 3 did not differ from group 1.

Dence that the likely mechanism for the prevention of thyroiditis by KCIO₄ + MNT was the reduction of thyroid iodine rather than indirect effects at other sites.

The suppression of OS thyroiditis by iodine depletion over time. The details of treatment with KCIO₄, MNT, and T₄ are provided in Table I utilizing the 5 mg KCIO₄ protocol. Infiltration and TgAb incidence data were analyzed by multiple Chi-square analyses and subjected to a Bonferroni correction. Because chicks in this experiment had either severe disease or no disease, infiltration data were expressed as the incidence of chicks with thyroid infiltrates > 50% infiltration. The mean value of the infiltration negative birds (< 50%) at 9 wk was 7.9%.

Iodine depletion obtained with injections of KCIO₄ + MNT and dietary additions of KCIO₄ + MNT + T₄ produced a dramatic suppression of disease for up to 9 wk, the longest time period studied when compared with control birds given T₄ alone. Most of the control birds had severe disease by 5 wk of age. Their incidence of infiltration was 7/10 compared with the iodine depleted birds that had 0/9 to 2/9 from 5 to 9 wk of age. TgAb (incidence > 25 units) showed a similar reduction. Control birds at 5 wk of age had antibodies in 8/10 birds, whereas iodine-depleted birds had antibodies in 0/9 or 1/9 from 5 to 9 wk of age. All experimental groups differed from the control group for infiltration incidence (P < 0.01) and TgAb incidence (P < 0.0005).

Effect of propylthiouracil (PTU) and aminothiouracil on thyroid function in normal strain birds. To determine the optimal dosage of PTU and aminothiouracil, preliminary experiments to determine their effects on iodine metabolism in normal birds were performed. Data were analyzed by ANOVA + Fisher PLSD at P < 0.05. Both PTU (0.1%) and aminothiouracil (0.2%) caused similar changes in ¹²⁵I uptake such as significantly increased iodide and decreased DIT and T₃ + T₄ indicative of inhibition of iodination and coupling. Aminothiouracil at 0.1% did not alter these parameters. Thyroid gland weight was significantly increased by all treatments including aminothiouracil at 0.1%, a concentration which did not block iodination. This may be indicative of an additional hypothalamic-pituitary site of aminothiouracil action.

Effect of various antithyroid drugs on thyroiditis in 6-wk-old OS chickens. PTU and aminothiouracil given in the diet from hatching significantly reduced thyroid infiltration (Table III, experiment 1). When KCIO₄ and MNT injections preceded the administration of dietary antithyroid drugs (experiment 2) a reduction in thyroidal infiltration and a decrease in the incidence of TgAb was again observed.

Effect of various antithyroid drugs on the immune response to foreign antigens in 6-wk-old OS chickens. To determine if antithyroid drugs decreased thyroiditis by causing generalized immunosuppression, we tested the effect of these drugs on the immune response to BGG, a T cell–dependent antigen, and to Brucella abortus, a T cell–independent antigen. Because hypothyroidism could have affected the immune responses to exogenous antigens, both control and experimental groups received thyroxine. PTU and aminothiouracil given in the diet from hatching (Table IV, experiment 1) did not cause a difference in the antibody response to BGG. When PTU, aminothiouracil, and KCIO₄ plus MNT were given in the diets of birds receiving KCIO₄ and MNT injections (experiment 2) the response to Brucella abortus was unaffected. There was also no decrease in antibody response to BGG in birds receiving KCIO₄, MNT, PTU, or ATA. However, for unknown reasons, there was a significant increase in the anti-BGG response in both the PTU and KCIO₄ plus MNT groups. It is possible that these drugs, by preventing the severe inflammatory autoimmune response, allowed the immune system to respond more vigorously to a foreign antigen.

Table III. Effect of Various Antithyroid Drug Regimens on Thyroiditis in OS Chickens

<table>
<thead>
<tr>
<th>In ovo and at hatching</th>
<th>Additions to diet</th>
<th>Infiltration incidence (incorporation &gt; 50%)</th>
<th>TgAb (incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>T₄</td>
<td>9/10</td>
<td>ND</td>
</tr>
<tr>
<td>None</td>
<td>T₄, PTU (0.1%)</td>
<td>4/11</td>
<td>ND</td>
</tr>
<tr>
<td>None</td>
<td>T₄, ATA (0.2%)</td>
<td>6/11</td>
<td>ND</td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCIO₄/MNT injection</td>
<td>T₄</td>
<td>7/10</td>
<td>9/10</td>
</tr>
<tr>
<td>KCIO₄/MNT injection</td>
<td>T₄, KCIO₄, MNT</td>
<td>1/9</td>
<td>2/8</td>
</tr>
<tr>
<td>KCIO₄/MNT injection</td>
<td>T₄, PTU (0.1%)</td>
<td>1/7</td>
<td>3/6</td>
</tr>
<tr>
<td>KCIO₄/MNT injection</td>
<td>T₄, ATA (0.2%)</td>
<td>2/8</td>
<td>3/8</td>
</tr>
</tbody>
</table>

OS chickens (8–11 per group) were placed on various antithyroid regimens at hatching plus T₄ (20 μg/100 g food) (experiment 1). In experiment 2 chickens were given KCIO₄ + MNT injections before the initiation of the dietary regimens. The data were analyzed by multiple Chi-square analyses and subjected to a Bonferroni correction. In experiment 1 PTU and aminothiouracil both reduced thyroid infiltration (P < 0.0002). In experiment 2, all dietary additions significantly reduced infiltration from the T₄-fed control (P < 0.015) and TgAb incidence (P < 0.001).
OS chickens were treated with various drug regimens as described in Table IV. The birds of experiment 1 were injected with bovine gamma globulin (1 mg in complete Freund adjuvant) at 4 wk and tested at 6 wk for antibody to BGG by ELISA. Birds of experiment 2 received a single injection of BGG (1 mg in CFA) at 3 wk and *Brucella abortus* (2.7 × 10⁵ bacilli) 4 d later. At 5 wk their sera were tested for antibodies. Data were analyzed by ANOVA + Fisher PLSD.

There were no differences in antibody titers to BGG in experiment 1, but in experiment 2 birds provided with dietary KCIO₄ + MNT or PTU (plus T₄) had more BGG Ab than control birds fed T₄ alone (P < 0.05). There were no differences between any groups in their response to *B. abortus*.

**The effect of dietary iodine on recipient target organ susceptibility to adoptive transfer of thyroiditis.** CS chickens develop minimal thyroiditis by 10 wk of age on a high-iodine diet (1) and would be expected to have even less disease upon treatment with cyclophosphamide. However, transfer of OS splenocytes to KI-treated CS recipients caused significant thyroidal infiltration (Table V). Transfer to iodine-depleted CS recipients, on the other hand, resulted in minimal infiltration. These treatment regimens had no effect on TgAb production.

**Discussion**

The present study provides the first experimental demonstration of the protective effect of iodine depletion in the development of autoimmune thyroiditis in an animal model. Our previous attempt to demonstrate this phenomenon in the OS chicken by KCIO₄-induced iodine depletion from the time of hatching was minimally successful (1). The iodine depletion regimen consisting of KCIO₄ and MNT treatments beginning in ovo and continuing after hatching caused a fivefold reduction in thyroidal iodine at hatching, reduced infiltration to 2% of untreated controls values and decreased TgAb production for as long as 9 wk. It was important to begin iodine depletion in ovo because treatment with these drugs at hatching resulted in only partial improvement. It was also necessary to maintain severe iodine deficiency by continuing KCIO₄ and MNT administration in the diet after hatching. Even when preceded by the in ovo treatment, KCIO₄ without MNT was ineffective in the present series of experiments. This may be an indication that the dose of KCIO₄ was not high enough to completely block the thyroidal uptake of dietary iodine. When the diet was supplemented with KI in an attempt to override the iodine deficiency induced by KCIO₄ and MNT, infiltration increased toward untreated control values demonstrating that the mode of action of KCIO₄ and MNT is the reduction of intrathyroidal iodine.

The amount of iodine taken up by the thyroid of embryonic OS chicks in our previous study was relatively high (1). At that time the normally hypothyroid OS breeding hens were fed prothamine, an iodinated casein that contains enough T₄ to render the hens euthyroid for breeding purposes. However, this diet caused a 4.5-fold increase in the iodine content of their eggs (12). Initially we reasoned that the birds were receiving a significantly increased iodine load in ovo that had a detrimental effect on their disease. However, when the OS flock at Cornell University was subsequently placed on a T₄-supplemented diet containing no prothamine they continued to have progressive disease. The present study shows that the iodine in a normal diet taken up by the thyroid during embryonic development is critical in the development of the disease.

Our results indicate that TSH does not play a major role in thyroiditis of OS chickens because significant amelioration was achieved in birds given KCIO₄ that had increased TSH shown by a fourfold increase in thyroid weight compared to T₄-fed animals. In addition, suppression of TSH by exogenous T₄ did not decrease thyroiditis. Weetman et al. (3, 13) also observed that treatment with T₄ did not influence experimental autoimmune thyroiditis in rats. Some studies, however, have reported a slight and/or transient effect of T₄ in reducing the disease of OS chickens (14, 15). However, neither of those studies addressed the question of whether T₄ acts by reducing TSH, intrathyroidal iodine, or both. The studies of Reinhardt et al. are of particular interest (16). They observed a reduction of thyroidal infiltration in BB/W rats with T₄ treatment for 2–3 mo. The protective effect of T₄ was lost when the rats were additionally treated with iodine, illustrating the key role of iodine in this disease.

The effect of PTU on Hashimoto's thyroiditis has been controversial. McGregor et al. (17) reported a decrease in thyroid autoantibodies in patients treated with carbimazole, however, this observation has not been confirmed. In fact, Jansson et al. (18) and Romaldi et al. (19) have shown that even high doses of antithyroid drugs fail to cause a diminution in autoantibody production. Rennie et al. (20) found lower autoantibody production in thyroglobulin-induced autoimmune thyroiditis in...
the rat, however, Davies could not confirm these findings in a similar model (21). In Graves’ disease where PTU-induced immunosuppression is well documented, the mechanism of action remains controversial (22). The results presented here show a clear ameliorative effect of PTU on thyroiditis of OS chickens.

To determine whether the effects of KClO₄, MNT, PTU, and aminotriazole were due to direct action on the thyroid or to generalized suppression of the immune system, we examined their effects on the responses to unrelated antigens. None of the antithyroid drugs decreased antibody responses to BGG, a T cell–dependent antigen or to B. abortus, a T cell–independent antigen. These results argue against a generalized effect on the immune system although they do not rule out the possibility of a local effect of the drugs on the immune cells within the thyroid. On the other hand, both PTU and aminotriazole inhibit iodine organification and may act by decreasing the iodine content of critical thyroidal components such as thyroglobulin as discussed below.

While this study clearly demonstrates that the uptake and metabolism of iodine is critical in the development of autoimmune thyroiditis, the mechanism underlying iodine action remains unclear. There is some evidence for a direct relationship between the iodine content of Tg and its immunogenicity. We have shown that highly iodinated thyroglobulin elicits a greater antibody response in normal chickens than poorly iodinated thyroglobulin (9). Champion et al. have demonstrated that the response to thyroglobulin by murine T cell hybridomas is directly related to its iodine content (23). They also showed that poorly iodinated thyroglobulin was ineffective in causing adjuvant-induced thyroiditis while normally iodinated thyroglobulin was able to induce the disease. However, in the spontaneous disease of OS chickens there is no evidence that highly iodinated Tg is a major etiologic factor. As far as the spontaneously occurring antibodies to Tg, we have recently shown that OS autoantibodies react well with thyroglobulin of high and low iodine content (9). Furthermore, the thyroglobulin from OS chickens contains less iodine than that of normal strains maintained on similar diets and suppressed with T₄ (24).

There is evidence that the iodination of Tg may not be the only mechanism by which iodine affects thyroiditis. Another possible mechanism of iodine action may involve free radical alteration of the thyroid gland. Iodine may interact with reactive oxygen intermediates such as H₂O₂ or O₂⁻ generated in the thyroid to produce highly reactive oxidized forms of iodine. We have shown that structurally unrelated dietary antioxidants reduce the onset and severity of thyroiditis in OS chickens (10). This suggests that oxidative alteration of the thyroid may play a role early in the development of the disease. Although increased free radical production in OS thyroids containing normal amounts of iodine has yet to be demonstrated, thionamide drugs have been shown to decrease free radical formation (25–27). However, while this may explain the action of PTU, the effect of aminotriazole, a catalase inhibitor, cannot be explained by this mechanism.

Finally, it is possible that iodine depletion by KClO₄ and MNT as well as inhibition of iodine metabolism by aminotriazole and PTU may decrease the formation of a putative iodine metabolite, unrelated to thyroglobulin, but important in the immune response. Using SDS/PAGE we failed to find an iodinated protein unique to OS thyroid (24), however, the possibility of a nonprotein iodine-dependent mediator remains.

The results of the adoptive transfer experiment reported here offers experimental evidence for the importance of acquired iodine-induced target organ alteration in the development of OS thyroiditis. Splenocytes sensitized to and specific for thyroid antigens transferred disease only in iodine sufficient recipients. This emphasizes the importance of iodine-induced thyroidal alteration before the autoimmune process begins. Such alteration could result in the expression of altered antigens or an increase in the expression of normal antigens. The precise mechanism remains to be elucidated.

Acknowledgments

This work was supported by National Institutes of Health grants DK-35846 and DK-20028 and training grant 5-T32-DC-00026 (A. Dhar).

References

Iodine Is Crucial for Obese Strain Thyroiditis