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Effects of Hydrogen Peroxide-Generating Systems on the Wolff-Chaikoff Effect*

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ABSTRACT. In bovine thyroid slices, the inhibition of organic binding of iodide by excess iodide in the range 5–10 μg/ml was prevented by incubating the slices in the presence of TSH. The Wolff-Chaikoff effect was also overcome by the presence of a hydrogen peroxide-generating system, such as glucose-glucose-oxidase or tyramine. TSH and hydrogen peroxide enhanced the synthesis of both iodotyrosines and iodothyronines. The enhanced organification of iodine in the presence of TSH or hydrogen peroxide was not due to an abrupt synthesis of organic iodine during the early phase of incubation before intrathyroidal iodide concentrations had reached the inhibitory levels. These findings suggest that the inhibition of organic binding of iodine in the presence of excess iodide may be due to a diminished generation or a decreased availability of hydrogen peroxide in the thyroid. (*Endocrinology* **109:** 2095, 1981)

INHIBITION of organic binding of iodide in the thyroid by excess iodide, the Wolff-Chaikoff effect, has been recognised for many years (1, 2). Various explanations have been proposed for the mechanism of this phenomenon (for a review see Ref. 3). TSH injected into rats produces both prompt stimulation of thyroid organic binding of iodine and increased resistance to induction of the Wolff-Chaikoff effect (4). Since the stimulating effect of TSH on organic binding has been ascribed to enhanced production or availability of hydrogen peroxide (5), experiments were carried out to study the effect of altered availability of hydrogen peroxide in the thyroid *in vitro* upon the occurrence of the Wolff-Chaikoff effect.

Materials and Methods

[^{131}I]Iodide (in NaOH solution; 2 mCi/ml) was obtained from Cambridge Nuclear, and [^{14}C]formate (SA, 50 mCi/mmol) was purchased from New England Nuclear Corp. (Boston, MA). Glucose oxidase (type V; 1200 U/ml) and tyramine were obtained from Sigma Chemical Co. (St. Louis, MO), and tranylcypromine sulfate was generously supplied by Smith, Kline, and French Laboratories (Philadelphia, PA). Bovine TSH (Thyropar) was obtained from Armour (Chicago, IL).

Fresh calf thyroids were obtained from a local abattoir. After freeing the thyroid lobe of capsular investments, thin slices were prepared with a Stadie-Riggs microtome; each slice weighed 50–75 mg. Only slices from a single lobe were used in each experiment.

Organic binding of iodine

Each calf thyroid slice was preincubated in a modified Krebs-Ringer phosphate solution (1.3 mM Ca^{2+} instead of 2.6 mM), pH 7.4, for 1 h and then transferred to incubate in individual flasks containing 2 mg glucose, 1 mg bovine serum albumin, 10 μCi Na^{131}I, and varying concentrations of iodide together with the test substances in 2 ml fresh Krebs-Ringer phosphate. In experiments in which thyroid tissues were subjected to pronase digestion after incubation for determination of iodoamino acid composition, the quantity of Na^{131}I was increased to 150 μCi/flask. Each flask was incubated with shaking for 45 min at 50 strokes/min at 37 C in air in a Dubnoff metabolic incubator. After incubation, the slices were removed, blotted with gauze, weighed, and homogenized with 0.5 ml aqueous methimazole (2 mM) in a Ten Broeck ground glass homogenizer (Kontes Co., Vineland, NJ). The total uptake of ^{131}I by the thyroid slice, the proportion of ^{131}I organically bound, and the amount of newly synthesized organic iodine as well as the iodoamino acid composition after pronase digestion were determined by the quantitative paper chromatographic procedures previously described (6).

In the experiments in which the effects of tranylcypromine sulfate were tested, the substance was present in both preincubation and incubation media.

[^{14}C]Formate oxidation

The procedure was carried out as previously described (7).

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Results

Effects of excess iodide on organic binding of iodine

The total iodine uptake by thryoid slices increased with increasing concentrations of iodide present in the medium over a range of 0.5–100 μg/ml (Fig. 1, *upper panel*). By contrast, newly formed organic iodine was found to reach a peak in slices incubated in medium containing 1–2 μg iodide/ml (Fig. 1, *lower panel*). There was a consistent and pronounced fall in organic iodine formation in slices incubated in medium containing 5–10 μg/ml iodide or more. It appeared that when the iodide concentration in the thyroid slices reached a concentration ranging, in different experiments, from 12.5–40 ng/mg tissue, the Wolff-Chaikoff phenomenon occurred.

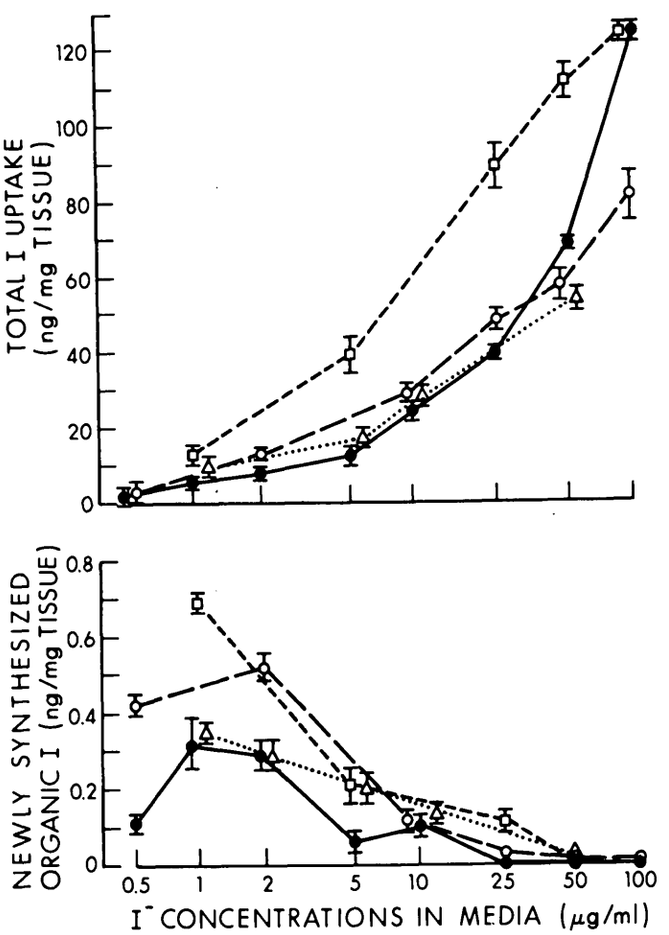

FIG. 1. Effects of increasing concentrations of I^- on uptake and organic binding of I^- in bovine thyroid slices. Individual bovine thyroid slices were incubated in 2 ml Krebs-Ringer phosphate containing 2 mg glucose, 1 mg bovine serum albumin, 10 μCi [^{131}I]iodide, and varying concentrations of iodide as KI (0.5–100 μg/ml) at pH 7.4 for 45 min. Each value represents the mean ± SEM of at least three incubations. Four separate experiments (identified by different symbols) are shown, each using tissue from a separate thyroid gland. The *upper panel* shows iodine accumulation; the *lower panel* shows newly formed organic iodine at the various iodide concentrations.

Effects of glucose-glucose oxidase on organic binding of iodine in the presence of excess iodide

When the hydrogen peroxide-generating system, glucose plus glucose oxidase, was present in the medium, no inhibition of organic binding of iodine was observed in thyroid slices incubated in medium containing iodide over a wide concentration range (1–100 μg/ml). As iodide concentrations in the medium rose, the total iodine uptake increased in both the presence and absence of glucose-glucose oxidase (Table 1). In the presence of glucose-glucose oxidase, organic iodine formation also increased steadily (Fig. 2, *upper panel*); the increase was observed in both iodotyrosines and iodothyronines (Fig. 2, *lower panel*).

Organic iodine formation was found to be greater in slices incubated in the presence of larger quantities of glucose oxidase (Fig. 3). In slices incubated in medium which contained a small quantity of glucose oxidase (0.05 μl/flask) sufficient to enhance organic binding by a few fold above the control, organic iodine formation reached a plateau at higher iodide concentrations, but no inhibition of organic binding was observed even at very high iodide concentrations.

Since a major portion of the organic iodine formation in the glucose-glucose oxidase experiments might have occurred in the early phase of incubation when the iodide concentrations in the slices might not have reached the critical high levels, kinetic studies were carried out to investigate such a possibility. Over the course of a 60-min incubation in which accumulated, newly synthesized organic iodine was determined at varying time intervals (15, 30, 45, and 60 min), organic iodine formation in the controls (*i.e.* no glucose oxidase present) was consistently higher at an iodide concentration of 1 μg/ml than at 5 μg/ml (Fig. 4, *lower panel*). By contrast, in presence of glucose oxidase, organic binding was greater at all time intervals in slices incubated with iodide at 5 μg/ml than at 1 μg/ml (Fig. 4, *upper panel*). In a separate experiment,

TABLE 1. Comparative effects of incubation in presence and absence of glucose oxidase upon the total iodine uptake by slices incubated with varying concentrations of iodide

Iodine conc. in medium (μg/ml)	Total iodine uptake by thyroid slices (ng/mg tissue)		*P* values
	No glucose oxidase	+ Glucose oxidase	
2	11.3 ± 0.90	13.3 ± 0.98	>0.05
7.5	30.7 ± 3.83	36.8 ± 0.60	>0.05
25	54.9 ± 4.67	75.2 ± 6.12	>0.05
50	83.7 ± 1.19	105.2 ± 10.21	>0.05
100	117.9 ± 5.01	150.5 ± 4.26	>0.05

Each value is the mean ± SEM of triplicate incubations. Incubation conditions were as described in Fig. 1.

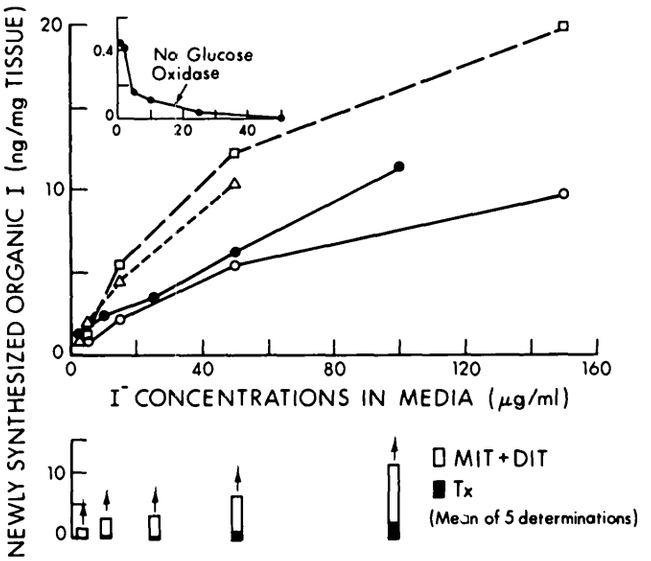

FIG. 2. Inhibition of the Wolff-Chaikoff effect in bovine thyroid slices in the presence of glucose-glucose oxidase in the medium. Incubation conditions were as described in Fig. 1 with 5 μl/flask glucose oxidase (1.2 U/μl) in the medium during incubation. Four separate experiments (identified by different symbols) are shown, each using tissue from a separate thyroid gland. The *small inset at the upper left* is a representative experiment without glucose oxidase. Each value is the mean of at least three incubations. The iodoamino acid composition of the newly formed organic iodine in the experiment (indicated by the *black circles*) is shown in the *lower panel.* Each *bar* represents the total newly formed organic iodine, iodotyrosines (MIT and DIT), and iodothyronines (Tx) at varying iodide concentrations in the medium (shown by the *arrows*).

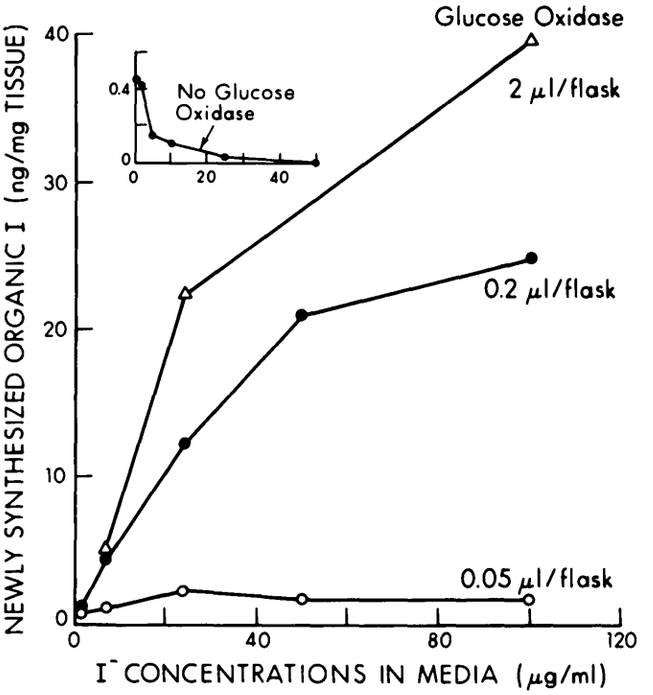

FIG. 3. Effects of adding various amounts of glucose oxidase to the medium on the Wolff-Chaikoff effect in thyroid slices. Incubation conditions were as described in Fig. 1, except for the presence of varying amounts of glucose oxidase (0.05, 0.2, and 2 μl/flask; 1.2 U/μl) during incubations. Each value represents the mean of three incubations.

in which glucose oxidase was added only after the initial 30 min of incubation in the presence of iodide and incubation was then continued for an additional 45 min, the inhibition of organic binding by high iodide levels was again clearly overcome in the presence of the glucose-glucose oxidase hydrogen peroxide-generating system (Table 2).

The possible contribution of nonenzymatic iodination by the action of hydrogen peroxide generated from glucose-glucose oxidase was assessed by experiments comparing iodination in control slices with that in slices that had been immersed for 10 min in boiling Krebs-Ringer phosphate solution before incubation. In such experiments (data not shown), organic iodine formation was consistently and greatly diminished in the boiled tissue, the newly formed organic iodine averaging approximately 10% of the corresponding values in the unboiled tissues over a range of iodide concentrations from 1-100 μg/ml in the medium. Thus, the magnitude of nonenzymatic iodination in thyroid slices in the presence of the hydrogen peroxide-generating system would appear to be insufficient to account for either the greatly augmented iodination or for the resistance to the Wolff-Chaikoff effect observed in slices incubated in the presence of glucose-glucose oxidase.

Effects of tyramine on organic binding of iodine in presence of excess iodide

Tyramine has been shown to stimulate the organic binding of iodine in the thyroid (8), presumably by generation of hydrogen peroxide via tissue monoamine oxidase. In the presence of tyramine (0.4 mM), organic iodine formation was enhanced in slices incubated at different iodide concentrations (Fig. 5, *left panel*). No clear-cut inhibition of organic binding by excess iodide was observed in two experiments, and some decline in organic iodine formation was noted in one experiment, but only at comparatively high iodine concentrations (25-50 μg/ml). In the presence of the monoamine oxidase inhibitor tranylcypromine sulfate (0.01 mM), this effect of tyramine was abolished, and the Wolff-Chaikoff phenomenon was again noted to occur at the usual iodide concentration of 5 μg/ml (Fig. 5, *right panel*).

Effect of TSH on iodide inhibition of organic binding

In the presence of TSH (50 mU/ml), organic iodine formation was greatly enhanced in thyroid slices incubated over a wide range of iodide concentrations (1-100

TABLE 2. Effects of glucose-glucose oxidase on organic binding of iodine

Incubation conditions	Total I uptake and organic I formation by thyroid slices (ng/mg tissue) incubated in medium containing iodide					
	1 μg I⁻/ml		10 μg I⁻/ml		100 μg I⁻/ml	
	Uptake	Organic I	Uptake	Organic I	Uptake	Organic I
A. Initial 30-min incubation	2.7 ± 0.03	0.17 ± 0.02	17.5 ± 1.07	0.03 ± 0.02	50.5 ± 2.10	0
B. Initial 30-min + additional 45-min incubation (no glucose oxidase)	5.03 ± 0.15	0.79 ± 0.02	24.1 ± 2.10	0.28 ± 0.04	58.1 ± 2.90	0.07 ± 0.02
C. Initial 30-min + additional 45-min incubation (5 μl/flask glucose oxidase added after initial 30-min incubation)	5.2 ± 0.44	1.29 ± 0.15	40.9 ± 3.05	13.40 ± 2.01	93.1 ± 6.46	23.61 ± 3.03

Three groups of thyroid slices (A, B, and C), prepared from a single thyroid lobe, were incubated in parallel in medium containing various concentrations of iodide (conditions as described in Fig. 1). Each value is the mean ± SEM of triplicate incubations.

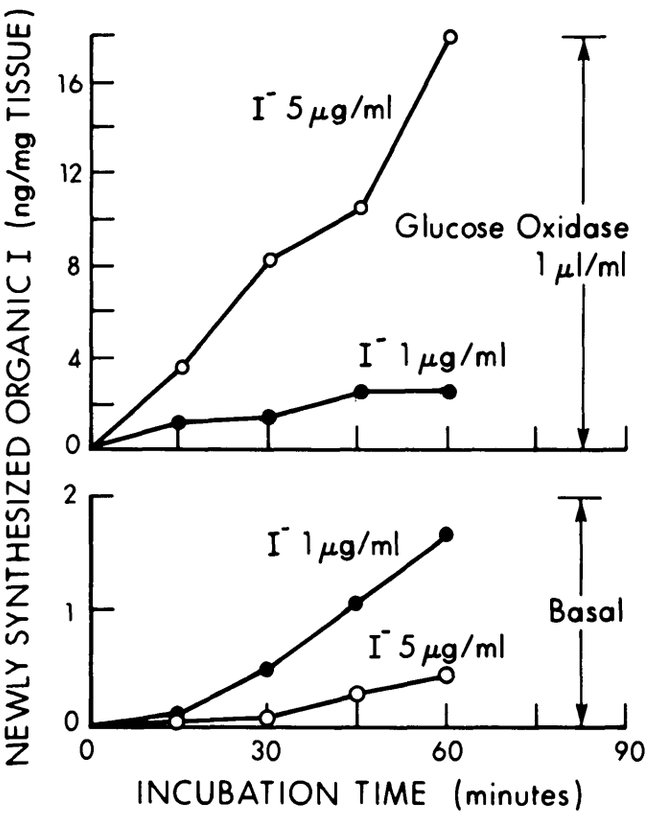

FIG. 4. Kinetic study of organic iodine formation in bovine thyroid slices in the presence and absence of glucose oxidase. Bovine thyroid slices were individually incubated in 2 ml Krebs-Ringer phosphate containing 2 mg glucose, 1 mg bovine serum albumin, 10 μCi ^{131}I, and 1 or 5 μg/ml I^- in the presence of 1 μl/ml (1.2 U/μl) glucose oxidase (*upper panel*) or in its absence (*lower panel*). Newly formed organic I^- was determined after incubation for 15, 30, 45, and 60 min. Each value represents the mean of three incubations.

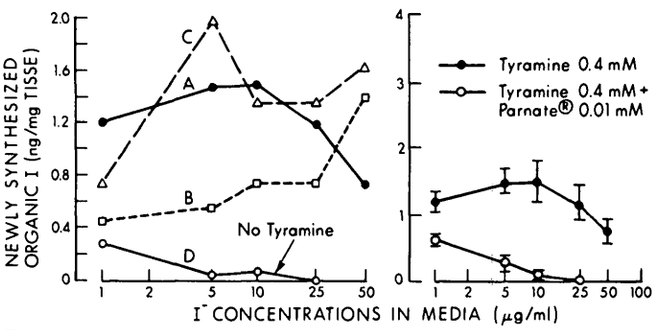

FIG. 5. Effects of tyramine on the Wolff-Chaikoff effect in bovine thyroid slices. *Left panel*, Incubation conditions were as described in Fig. 1. Four separate experiments are shown. In A, B, and C, tyramine (0.4 mM) was present in the incubation medium, while in D, no tyramine was added. *Right panel*, Thyroid slices were incubated in 0.4 mM tyramine, with and without tranylcypromine (Parnate; 0.01 mM). Each value is the mean of at least three incubations.

μg/ml; Fig. 6). In one experiment, no inhibition of organic binding was observed even at very high iodide concentrations. In the other experiments, some inhibition of organic iodine formation was noted at an iodide concentration of 10 μg/ml in one experiment and at 50 μg/ml in another experiment, and there was only a slight decline from peak organic binding observed at an iodide concentration of 100 μg/ml in the third experiment. In all instances, organic iodine formation in the presence of TSH at any (including the highest) iodide concentration tested was greater than the peak value in the absence of TSH. Similar results were obtained in experiments in which thyroid slices were preincubated with iodide before the addition of TSH.

Effects of iodide on formate oxidation in thyroid

Attempts were made to assess hydrogen peroxide production indirectly via formate oxidation in thyroid slices at levels of iodide found to inhibit organic binding. [^{14}C] Formate oxidation was measured in slices incubated in medium containing 1 μg/ml iodide (the concentration which usually yielded peak organic iodine formation) and also 10 μg/ml iodide (a concentration which usually inhibited organic binding). Formate oxidation was found to

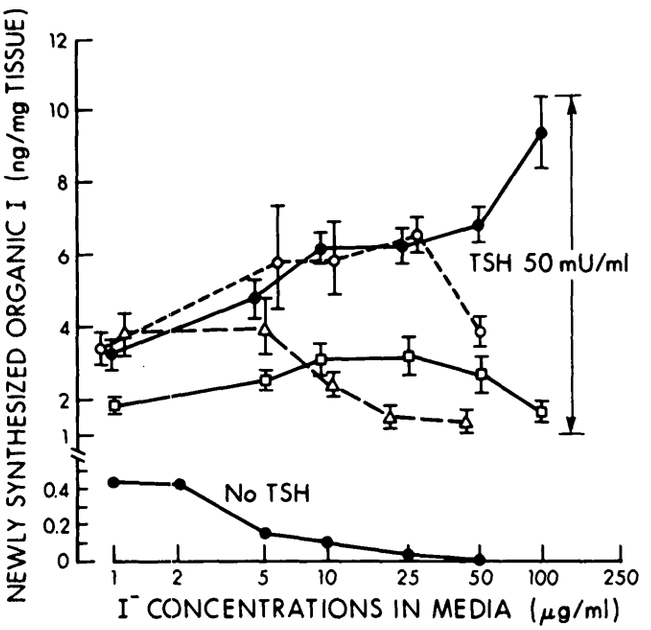

FIG. 6. Effects of TSH on the Wolff-Chaikoff effect on bovine thyroid slices. Incubation conditions were as described in Fig. 1, in the presence and absence of 50 mU/ml TSH in the incubation medium. Four separate experiments (identified by different symbols) are shown, each using tissue from a separate thyroid gland. The experiment (shown by the *black circles*) was performed in the presence and absence of TSH. Each value represents the mean ± SEM of at least three incubations.

TABLE 3. Comparative effect of incubation in presence of 1 μg/ml iodide *vs.* 10 μg/ml iodide on formate oxidation by bovine thyroid slices

Exp	Addition	$^{14}CO_2$ formed (cpm/100 mg tissue) by thyroid slices incubated in medium containing iodide		*P* values
		1 μg/ml	10 μg/ml	
A	None (5)	287 ± 5	237 ± 12	<0.01
B	None (10)	150 ± 15	131 ± 12	>0.05
C	None (6)	224 ± 11	201 ± 6	>0.05
D	None (5)	318 ± 15	283 ± 12	>0.05
E	50 mU/ml TSH (5)	414 ± 17	384 ± 21	>0.05

Slices were preincubated individually in 2 ml Krebs-Ringer bicarbonate solution containing iodide (1 or 10 μg/ml) for 30 min, then were transferred to 2 ml fresh Krebs-Ringer bicarbonate solution containing 2 mg glucose, 1 mg albumin, [^{14}C]formate (0.5 μCi in 0.5 μmol), and iodide (KI; 1 or 10 μg/ml), and incubated for 45 min. The numbers in parentheses are the number of incubations.

be consistently lower by 10–15% when the slices were incubated with 10 μg/ml iodide compared with 1 μg/ml iodide in both the presence and absence of TSH (Table 3). However, the difference was not statistically significant.

Discussion

It is generally accepted that intrathyroidal organification of iodine is mediated through a peroxidase-hydrogen peroxide system. The inhibition of organic binding of iodine observed at high plasma and intrathyroid iodide concentrations (Wolff-Chaikoff effect) has variously been attributed to: 1) competition between iodination of protein and that of iodide (*i.e.* I_2 formation), the latter being favored in presence of excess iodide (9, 10); 2) oxidation of thyroid pyridine nucleotides by excess iodide (11), with the implication that the generation of hydrogen peroxide may be thereby diminished because of less availability of reduced pyridine nucleotide as a source of hydrogen peroxide; 3) a disturbance in the favored critical ratio of the concentrations of iodide and newly formed iodoproteins (12); and 4) the inhibition of adenylate cyclase when thyroid iodide concentration is increased, an effect mediated by a product of iodide oxidation, which reaches a critical level when the intrathyroidal iodide concentration is high (13).

Our data indicate that at elevated intrathyroidal iodide concentrations there may be a decreased availability of hydrogen peroxide for iodination reactions. This conclusion is based on the observation that the inhibitory effects of excess iodide on the iodination of thyroprotein could be overcome when the thyroid slices were incubated in the presence of agents that are known to generate hydrogen peroxide, *e.g.* glucose-glucose-oxidase, tyramine, or TSH. Whether this apparent decreased availability of hydrogen peroxide induced by excess iodide is due to an increased utilization of hydrogen peroxide through such competing reactions as I_2 formation in the presence of excess I^- or to decreased formation of hydrogen peroxide through inhibition of the intrathyroidal hydrogen peroxide-generating system by excess iodide remains to be determined. The second alternative is suggested by the studies of Yamamato and DeGroot (14), who could not demonstrate any inhibition by excess iodide of peroxidase-catalyzed iodination reactions, suggesting that impaired generation of hydrogen peroxide might be a factor in the Wolff-Chaikoff phenomenon.

The release from the inhibitory effects of iodide noted in the presence of externally added H_2O_2 is apparently not due to a reduction in iodide transport and a consequent decline in I^- concentrations in the slices, a mechanism that has been proposed for the phenomenon of escape from the Wolff-Chaikoff effect (15). The data presented in Table 1 show an actual enhancement of I^- uptake over a wide range of iodide concentrations when the slices were incubated in the presence of glucose-glucose oxidase. The kinetic studies shown in Fig. 4 and Table 2 also revealed that the enhanced organic binding in the presence of glucose-glucose oxidase was sustained, time dependent, and apparently not due to an abrupt initial synthesis of a large amount of organic iodine, as might have occurred in the early phase of incubation when iodide concentrations in the slices had not reached maximal or inhibitory levels.

The presence of TSH in the incubation medium stimulated organic iodine formation in thyroid slices over a

wide range of iodine concentrations (1–100 μg/ml). Iodide inhibition of organic binding in the basal state was readily overcome by TSH; indeed, organic iodine formation was greatly enhanced. However, our data do not exclude the possibility that iodide might have an inhibitory effect upon organic binding of iodine stimulated by TSH, but suggest that such inhibition might require iodide concentrations much higher than those at which the Wolff-Chaikoff phenomenon is observed in the absence of TSH. These results, showing a resistance to the induction of the Wolff-Chaikoff effect *in vitro* in the presence of TSH, would seem at first glance to be at variance with other well established findings that highly stimulated thyroid glands in both man (16–18) and rats (19) appear to be more sensitive to the inhibitory effect of iodide. However, it should be pointed out that our experimental conditions involve only brief acute exposure to TSH (incubation for 45 min) and are thus comparable to those of Rosenfeld and Rosenberg (4), who found prompt resistance to induction of the Wolff-Chaikoff effect in rats by acute TSH injection. It is indeed conceivable that the effects of acute and chronic stimulation of the thyroid might well be different, judging from the reported difference in iodide transport (20, 21), sensitivity to TSH (22, 23), and responses to iodide loads in acutely and chronically stimulated glands.

Our findings of a severalfold increase of newly formed organic iodine in the presence of glucose-glucose oxidase at both normal and excess levels of I^- suggest that hydrogen peroxide availability may be the rate-limiting step in organic iodination and hormone formation. While it is conceivable that the hydrogen peroxide generated via glucose-glucose oxidase in the medium stimulated organic iodine formation via mechanisms different from those used by the normal basal gland or in the presence of TSH, this seems unlikely since 1) the enhanced organic binding in the presence of glucose-glucose oxidase was concentration dependent and included new synthesis of iodothyronines as well as iodotyrosines; 2) findings similar to the inhibitory effect of glucose-glucose oxidase on the Wolff-Chaikoff effect were observed with tyramine, which can generate hydrogen peroxide via thyroidal monoamine oxidase, and its effect was blocked by monoamine oxidase inhibition, and 3) TSH, which acutely increases hydrogen peroxide formation and iodination, has been shown to have a similar effect *in vivo* to increase resistance to induction of the Wolff-Chaikoff phenomenon (4).

The mechanisms by which excess iodide influences the availability of hydrogen peroxide for iodination reactions remains to be determined. Although a decreased generation of hydrogen peroxide in the presence of excess iodide could not be demonstrated in these studies, the index used (formate oxidation) may not have been sensitive enough to measure small changes in concentrations of hydrogen peroxide under these experimental conditions. Since TSH-induced enhancement of hydrogen peroxide production in the thyroid is considered to be mediated through the stimulation of adenylate cyclase (5), the observations of Van Sande *et al.* (13) and Rapoport *et al.* (24) on the inhibition of adenylate cyclase by an oxidized form of iodide when intrathyroidal iodide concentrations are increased are of particular interest.

Our observations raise the possibility that at excess I^- levels, a decrease in cAMP formation occurs which leads to some diminution of intrathyroidal hydrogen peroxide production and organic binding. The inhibitory effect of iodide upon the release of glandular hormonal iodine cannot be explained solely by such a mechanism, however, since it is well established that the inhibition of hormonal release by excess iodide is not blocked by propylthiouracil and methimazole [which do block the effects of excess iodide on adenylate cyclase (25)]; these considerations may not apply to the Wolff-Chaikoff effect, which, for its study, precludes the use of antithyroid drugs.

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