Effect of chronic ingestion of sodium acetate on thyroid function

M. Goldman

Department of Biology, University of South Dakota, Vermillion (South Dakota 57069, USA), 25 August 1980

Summary. Chronic ingestion of sodium acetate over a 3-month interval may have an inhibitory effect on some aspect of organification of iodine and consequent synthesis of thyroid hormones.

It has been reported that sodium acetate exerts an antifertility action in rats, mice, hamsters, guinea-pigs and rabbits[1]. In preliminary experiments in our laboratory, we have been unable to demonstrate that the antifertility activity of sodium acetate is mediated through the pituitary-gonadal axis. Although unilateral gonadectomized rats of either sex treated with sodium acetate consistently showed no reduction in unilateral compensatory gonadal hypertrophy or diminution in organ weights of gonadal accessory target tissues, a decrease in thyroid weight was observed in both male and female hemicastrated rats treated with sodium acetate. The present study was initiated to investigate the effect of sodium acetate on thyroid function.

Materials and methods. Male Long-Evans rats (123–136 g) were randomly divided into 2 groups which received, Purina laboratory chow ad libitum, supplemented respectively with 0 or sodium acetate (NaAc), 300 mg/kg, which had been mixed thoroughly into the finely ground diet. The investigation was terminated 3 months later and several indices of thyroid function examined. 10 rats from each group were injected i.p. with 10 µCi of carrier-free ^{131}I and the 24-h thyroidal ^{131}I uptake, and chromatographic analyses of thyroid pronase hydrolysates were determined using the procedure of Goldman[2]. Serum levels of T_4 were determined in these rats on aliquots of blood obtained prior to injection of ^{131}I by radioimmunoassay using a commercially obtainable kit (Wien Laboratories, Succasunna, NJ). Serum TSH was measured by radioimmunoassay using the rat TSH kit supplied by the Rat Pituitary Hormone Program of the NIAMDD. The acute response to a single large iodide load (200 µg iodide) by the thyroid gland on changes in thyroid hormone synthesis due to decreased organic binding of iodide was also examined in 10 additional rats of each group using the procedure of Rosenfeld and Rosenberg[3] as modified by Goldman[2].

Results. The quantity of sodium acetate ingested was estimated from the food intake to be 21.0 mg/kg b.wt/day. A marked reduction in body weight ($p < 0.001$) was noted in rats that had ingested sodium acetate (table 1) and this was associated with a marked increase in 24-h radioiodine uptake, $p < 0.01$ (table 1). The increase in absolute organ weight for thyroid glands in sodium acetate-treated rats was even more significant when the relative thyroid weights of controls, 4.7 mg/100 g b.wt, were compared with that of the treated rats, 8.1 mg/100 g b.wt. Although there was no significant difference in the circulatory levels of serum T_4 in control and sodium acetate-treated groups (table 1), a significant increase in serum TSH ($p < 0.001$) was observed in rats that had been treated with sodium acetate.

Chromatographic analyses of thyroid hydrolysates illustrating the distribution of iodinated compounds are shown in

Table 1. Effect of sodium acetate on body weight, thyroid weight, 24-h thyroid ^{131}Iuptake, and circulatory T_4 levels in male Long-Evans rats

Group	No. of rats	Body weight (g)	Thyroid weight (g)	^{131}I uptake (% inject dose)	T_4 (µg/100 ml)	Serum TSH (mU/100 ml)
Control	10	379.8±9.4[a]	18.0±1.2	8.9±1.0	3.1±0.43	24.2±4.3
NaAc	10	298.2±12.1[c]	24.1±1.5[b]	18.9±2.1[c]	2.3±0.61	53.2±4.5[c]

[a] Mean value±SE. [b] Differs from control group, $p < 0.01$ as determined by Student's t-test. [c] Differs from control group, $p < 0.001$ as determined by Student's t-test.

Table 2. Distribution of ^{131}I (%) in chromatograms of thyroid hydrolysates in male Long-Evans rats[a]

Group	No. of rats	Origin	MIT	DIT	T_4	T_3	^{131}I	T_3:T_4
Control	8	3.9±0.7[b]	19.2±1.1	50.4±0.6	19.2±1.0	2.2±0.3	5.1±0.7	0.115±0.01
NaAc	8	4.4±0.4	18.7±0.8	49.6±1.0	20.7±0.7	1.3±0.1[c]	5.3±0.5	0.063±0.01[d]

[a] MIT: monoiodotyrosine; DIT: diiodotyrosine; T_3: triiodothyronine; T_4: thyroxine. [b] Mean±SE. [c] Significantly different from controls; $p < 0.05$. [d] Significantly different from controls; $p < 0.01$.

Table 3. Effect of sodium acetate on organification of an injected iodide load (200 µg) in male Long-Evans rats[a]

Group	No. of rats	^{131}I organically bound (%)	Organic iodine newly formed (ng/mg)	Inorganic iodide accumulated (ng/mg)
Control	10	77.2±6.7[b]	27.2±3.7	10.7±2.1
NaAc	10	47.5±3.9[d]	15.2±2.0[c]	16.7±1.7

[a] Rats received an i.p. injection of 20 µCi ^{131}I plus 200 µg carrier iodide and thyroid glands removed 1 h later, homogenized, chromatographed and the concentration of newly formed organic iodine and iodide calculated. [b] Mean value±SE. [c] Differs from control group, $p < 0.05$ as determined by Student's t-test. [d] Differs from control group, $p < 0.01$ as determined by Student's t-test.

table 2. No disparities in labeling of iodotyrosines (MIT and DIT) were noted. While no alteration in extent of labeling of the tetraiodothyronine (T_4) was observed, a significant diminution in labeling occurred in the iodothyronine, T_3, in rats maintained on sodium acetate ($p < 0.05$). This resulted in a decrease in the T_3:T_4 ratio ($p < 0.01$) below that of the control group. The data presented in table 3 show that the fraction of ^{131}I organically bound ($p < 0.01$) and the accumulation of newly formed thyroid hormone ($p < 0.05$) was significantly reduced in rats ingesting sodium acetate when subjected to the stress of an acute iodide load.

Discussion. Dietary ingestion of sodium acetate for 3 months caused a significant reduction in body weights of male Long-Evans rats. While thyroid gland weights of sodium acetate treated rats were increased significantly above the glands of control rats, thyroid weight related to body weight was almost double that observed in control rats. Moreover, thyroidal ^{131}I uptake was also markedly increased in treated rats but the circulating T_4 levels were not significantly different from the serum T_4 levels observed in the control group. The enhancement in thyrotropic activity evidenced by the elevated serum TSH levels in rats ingesting sodium acetate was responsible for the increases in thyroid weight and thyroid uptake of radioiodine. The administration of an iodide load resulted in a reduction in the capacity to organify iodide by the sodium acetate-treated rats. Moreover, chromatographic analyses of thyroid hydrolysates of rats ingesting sodium acetate revealed a significant decrease in labeling of T_3. Since labeling of T_4 was unaffected, this finding may indicate a coupling defect in the synthesis of T_3 with consequent reduction in T_3:T_4 ratios in rats chronically ingesting sodium acetate.

The view that the iodoamino composition of thyroglobulin is directly related to the iodine content[4,5] has been challenged recently by several investigators[6,7] who have suggested that additional factors such as the conformation of the thyroglobulin molecule, availability of tyrosyl residues for iodination, appropriate positioning of iodotyrosyl residues for coupling in the formation of the thyroid hormones (T_4 and T_3), pH, temperature and other factors may be important in determining the iodothyronine distribution in thyroglobulin with consequent altered T_3:T_4 ratios. Indeed, we have recently reported that chronic ingestion of mercuric chloride caused a significant reduction in percentage of labeled T_3 in rat thyroid hydrolysates perhaps reflecting a coupling defect exerted by mercury[8].

1 N.K. Dutta and G.R. Fernando, Indian J. med. Res. *60*, 48 (1972).
2 M. Goldman, Toxic. appl. Pharmac. *24*, 73 (1973).
3 P.S. Rosenfeld and I.N. Rosenberg, Endocrinology *78*, 621 (1966).
4 K. Inoue and A. Taurog, Endocrinology *83*, 279 (1968).
5 M. Rolland, M.-F. Montfort, L. Valenta and S. Lissitsky, Clin. chim. Acta *39*, 95 (1972).
6 M. Izumi and P.R. Larsen, J. clin. Invest. *59*, 1105 (1977).
7 A. Taurog and T. Nakashima, Endocrinology *103*, 632 (1978).
8 M. Goldman and P. Blackburn, Toxic. appl. Pharmac. *48*, 49 (1979).

Adaptation of the pituitary gland to prolonged LRH stimulation

T.R. Koiter, N. Pols-Valkhof and G.A. Schuiling

Department of Experimental Endocrinology, University of Groningen, 1 Bloemsingel, 9713 BZ Groningen (The Netherlands), 21 April 1981

Summary. With prolonged constant rate infusion of luteinizing hormone-releasing hormone (LRH), the LH secretion rate of the rat pituitary gland changes continuously until a steady state of relative desensitization has developed. Recovery from this state can occur independently from changes in the pituitary's LH content.

Luteinizing hormone-releasing hormone (LRH) and related agonistic substances can stimulate the pituitary gonadotrophs to release LH. Upon prolonged exposure to these substances, however, the rate of LH release decreases[1-5]. This decrease is not due to a genuine exhaustion of the pituitary LH store, but rather to progressive desensitization of the gonadotrophs for these stimulatory agents. This desensitization, possibly caused by receptor-down-regulation[6,7], however, may be accompanied by a marked depletion of the pituitary LH store[8].

In the present study, attention was payed to the relationship between LRH-induced changes in pituitary LRH-responsiveness and LH content.

Materials and methods. 8-week-old female Wistar rats were ovariectomized and used for experiments 5 weeks later. At the time they weighed 200–250 g. Prolonged stimulation of

Table 1. Analysis of data of figure 1. Integrated LH release (area under the curve; AUC(24); mean ± SEM) and the maximal plasma LH concentration (MH; ng LH-RP-1; mean ± SEM) during the 1st 24 h of a 48-h first infusion (of saline or 52 ng LRH/h and during the 24 h of a 2nd infusion of LRH at the rate of 416 ng/h. Integrated LH release (AUC(72); mean ± SEM) during the complete 72-h experimental infusion period. LH content (μg LH-RP-1; mean ± SEM) of the pituitary gland at the end of the experiment

1st infusion (material)	n	1st infusion (LH response) AUC(24)	MH	2nd infusion (LH response) AUC(24)	MH	AUC(72) (LH response)	Pituitary LH-content after experiment
Saline	7	107 ± 8^a	675 ± 129^a	656 ± 96^a	6720 ± 818^a	850 ± 105	611 ± 33
LRH	7	331 ± 28^b	2905 ± 195^b	471 ± 35^b	3968 ± 565^b	933 ± 63	601 ± 45

For each column holds p(a vs b) < 0.01. No differences in last 2 columns.