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Chronic Cassava Toxicity

Proceedings of an interdisciplinary workshop
London, England, 29-30 January 1973

Editors: Barry Nestel and Reginald MacIntyre

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Mechanism of the Goitrogenic Action of Cassava[1,2]

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ERMANS, A. M., M. VAN DER VELDEN, J. KINTHAERT, AND F. DELANGE. 1973. Mechanism of the goitrogenic action of cassava, p. 153–157. *In* Chronic cassava toxicity: proceedings of an interdisciplinary workshop, London, England, 29–30 January 1973. Int. Develop. Res. Centre Monogr. IDRC-010e.

Abstract Long-term action of cassava tubers added to a Remington diet has been tested in rats and compared with the supplementation of graded doses of thiocyanate. Both cassava and thiocyanate induce firstly: depletion of the thyroidal iodine stores, major abnormalities of intrathyroidal metabolism, reduction of plasma PB I^{127} and, secondly, moderate increase of plasma thiocyanate and a striking increase of plasma ^{35}SCN turnover. Thyroidal ^{131}I uptake is not inhibited at all. All findings show a qualitative and quantitative similarity between the effects of 10 g of cassava tubers and 1–2 mg of SCN.

It is concluded that a) the antithyroid action of cassava is caused by the endogenous production of SCN related to the conversion of cyanide, and b) in rats overloaded with large doses of SCN a renal adaptation mechanism is induced which strikingly reduces the plasma level of SCN.

Résumé Les auteurs ont mesuré sur des rats l'action à long terme de l'addition de tubercules de manioc au régime de Remington, et l'ont comparé aux effets d'un supplément dosé de thiocyanate. Le manioc, tout comme le thiocyanate, provoque en premier lieu: épuisement des réserves d'iode de la thyroïde, anomalies majeures du métabolisme intrathyroïdien, réduction du PB I^{127} dans le plasma et, en second lieu, augmentation modérée du thiocyanate plasmatique et augmentation frappante du taux de renouvellement du ^{35}SCN plasmatique. La captation de ^{131}I par la thyroïde n'est aucunement paralysée. Les résultats s'accordent à démontrer des ressemblances qualitatives et quantatives entre les effets de 10 g de tubercules de manioc et 1 ou 2 mg de SCN.

Les auteurs en concluent que a) l'action antithyroïdienne du manioc est due à la production endogène de SCN associée à la conversion du cyanure, et b) la surcharge de fortes doses de SCN met en branle, chez le rat, un mécanisme d'adaptation rénale qui réduit de façon frappante le niveau de SCN dans le plasma.

CLINICAL and experimental data reported in Delange et al. (1973) suggest that the antithyroid activity of cassava could be related to the conversion of its cyanide content into thiocyanate (SCN) after consumption by humans. However, such an hypothesis seems difficult to accept according to some observations recorded in individuals living in endemic goiter areas as well with current concepts concerning the metabolism of SCN.

Firstly, administration of a single dose of SCN in rats induces a marked increase of its concentration in plasma; concomitantly, iodide uptake in the thyroid gland is partially or completely

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blocked (Wollman 1962). Secondly, SCN ion is excreted very slowly in urine and its catabolic rate is very low (Sollman 1957). Prolonged ingestion of foodstuffs containing SCN precursors would be therefore expected to induce long-term increases of plasma SCN levels, and subsequently a persistent reduction of the iodide uptake in the thyroid gland should be observed. This view disagrees with the elevated values of ^{131}I uptake found in all severe goiter endemics and particularly in the Idjwi Island (Delange et al. 1968) in which one of the authors (F.D.) suggested that cassava could play a determining role in the development of the disease (Delange and Ermans 1971).

Few experimental data are available on the long-term influence of continuous administration of SCN or its precursors. The purpose of the present study was to reevaluate the modifications of SCN and iodine metabolism in rats submitted over a long period to a diet containing either cassava or graded doses of SCN (Ermans et al. 1972).

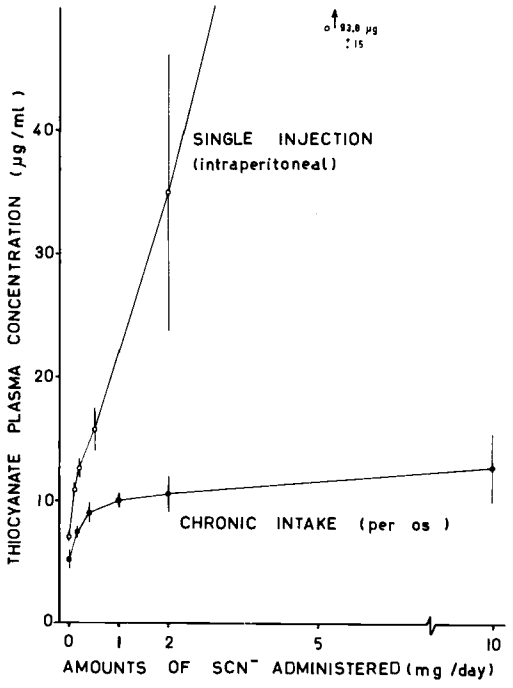

FIG. 1. Thiocyanate levels in serum of rats fed a Remington diet after administration of SCN doses ranging from 0.1 to 5.0 mg. A single intraperitoneal dose of SCN is administered in "acute experiments"; in "chronic experiments," the same dose is mixed every day with the Remington diet for 4 weeks (from Ermans et al. 1972).

Materials and Methods

The basic experimental protocol consisted in estimating various parameters of iodine and thiocyanate metabolism in 250 male White Star rats subjected to a low-iodine diet (Remington), supplemented with varying doses of thiocyanates ranging from 0.1 to 10 mg/day over a period of 4–6 weeks. The same estimations were made in rats subjected to a similar diet with the addition of 10 g of fresh cassava roots per day. Control experiments were carried out after a single intraperitoneal injection of the same doses of SCN. Some investigations were conducted after continuous supplementation with 10 µg of iodide per day.

At the end of the administration of the various diets, the following parameters were estimated for SCN distribution: plasma SCN concentration; urinary SCN excretion; SCN renal clearance; and disposal rate of plasma ^{35}S-labelled SCN. Also estimated were the parameters for iodine metabolism: thyroid ^{131}I uptake (4 h); iodide thyroid clearance; iodide renal clearance; iodine thyroid content; plasma PB ^{127}I; and pattern of thyroid hormone synthesis.

Results

Modifications of SCN Distribution Induced by Overload

Figure 1 shows a striking difference between the plasma levels of SCN under acute and chronic conditions. Four hours after a single intraperitoneal injection of SCN, with doses ranging from 1 to 5 mg, a sharp increase of SCN plasma levels takes place, whereas only a moderate increase of this level, to about 10 µg/ml, is observed (regardless of dosage) when thiocyanate is administered orally every day for several weeks. These samples were collected in the post-absorption period (Table 1); moderately higher values were observed during the feeding period (Table 2).

In investigating chronic effects (Table 1), almost the entire supplement of SCN (85%) is recovered in the urine. Renal clearances of SCN (Table 2) as well as the plasma disposal rate of ^{35}S-labelled thiocyanate (Table 1) are strikingly increased;

TABLE 1. Modifications of iodine and thiocyanate metabolism induced by prolonged administration of cassava or graded doses of thiocyanate. (Mean calculated on the basis of 5–9 individual values. Value statistically different from the control value: $*P < 0.01$; $**P < 0.001$.)

	Controls	SCN supplement (*mg/day*) 1	2	5	10	Cassava (*10 g/day*)
Thyroid I content[a] (*μg*)	1.0	0.7	0.6*	–	–	0.5**
Thyroid I content[b] (*μg*)	11.9	10.5	7.9**	7.6**	–	9.2**
^{131}I thyroid uptake[a,b] (*4 h, %/dose*)	8.5	11.2**	10.2	13.3**	–	9.7
Plasma PB^{127}I	1.8	1.3**	1.2**	–	–	1.1**
^{125}I-labelled iodoamino acids in thyroid glands						
MIT:DIT	0.89	1.31**	1.62**	–	2.00**	1.63**
as T4 (%)	21.0	18.0	11.0**	–	6.0**	13.0**
as T3 (%)	9.0	10.0	11.0	–	13.0	9.0
^{35}SCN plasma disposal rate (*fraction/h*)	0.01	0.05	0.14	0.22	–	0.13

[a]Estimates carried out during post-absorption period.
[b]Diets supplemented with iodide (10 *μg* day).

TABLE 2. Kinetics of iodide and thiocyanate after prolonged administration of SCN. Investigations were carried out during the feeding period.

	Controls	SCN supplement/day 1 mg	5 mg
SCN plasma concn (*μg*/ml)	5.3	10.6**	22.8**
Renal clearance of SCN (10^{-2} ml/min)	0.44	4.20**	15.03**
Renal clearance of iodide (10^{-2} ml/min)	6.7	8.2	9.3**
Thyroidal clearance of iodide (10^{-2} ml/min)	1.5	1.4	1.2**
Thyroid ^{131}I uptake (%/day, 4 h)	5.4	5.6	4.3

modifications of both parameters are found to be strictly related to the size of SCN intake.

Modifications of Iodine Metabolism Induced by SCN Overload

No inhibitory effect of the ^{131}I thyroid uptakes was evidenced during the post-absorption period in chronic toxicity experiments. For most of the SCN doses used, ^{131}I uptake was significantly increased (Table 1). A transient partial inhibition was, however, observed during the feeding period in the 5-mg group. In the same animals, the renal clearance of iodide was significantly increased (Table 2).

Iodine content of the thyroid glands was markedly decreased after chronic overload with large doses of SCN; the extent of the iodine depletion is proportional to the dose given and appears definitely more severe in iodine-deficient rats (Table 1). In the latter condition, marked abnormalities of the distribution of ^{125}I-labelled iodoamino acids were observed in the thyroid glands (Table 1), i.e. an increase of the monoiodotyrosine: diiodotyrosine (MIT:DIT) ratio and a decrease of thyroxine (T4) content; on the contrary, triiodotyrosine (T3) content remains unmodified in the same experimental conditions. The extent of the modifications of the MIT:DIT ratio and of the T4 content was also found depending quantitatively on the size of the SCN dose. Chronic SCN overload also induces a marked reduction of the plasma protein-bound iodine (PB^{127}I).

Modifications Induced by Chronic Feeding with Cassava

Chronic administration of cassava to rats significantly increases SCN concentration as well as the ^{35}S-labelled SCN disposal rate, in plasma. The value of the disposal rate (0.13/h) coincides with that obtained for the rats (Table 1) fed 2 mg SCN daily (0.12/h).

Modifications of the iodine metabolism were iodine depletion of the thyroid glands with increased MIT:DIT ratio and decreased T4 content and at least decrease of the plasma PB^{127}I (Table 1). No inhibitory effect of ^{131}I thyroid uptake was evidenced.

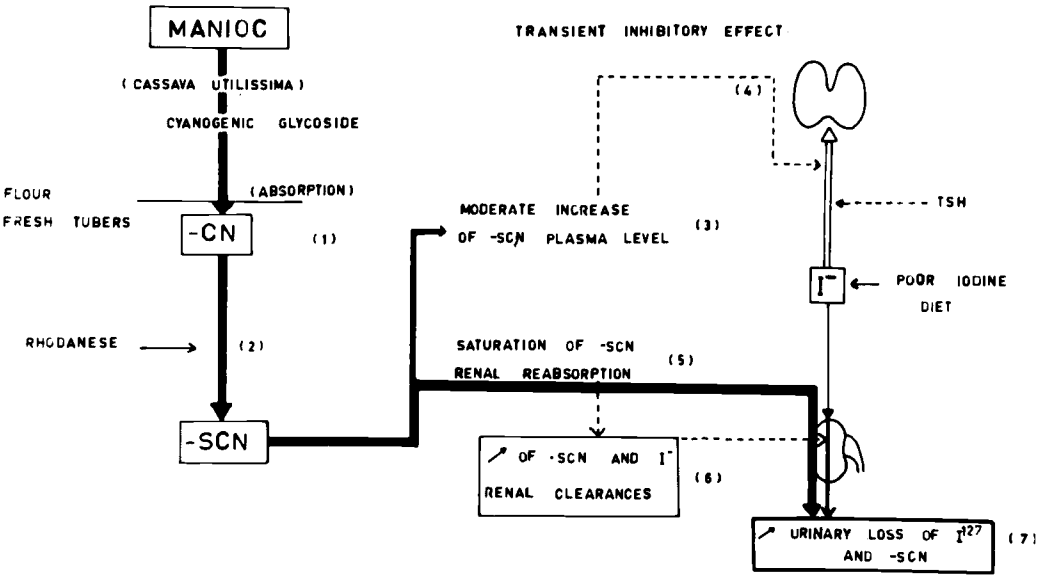

FIG. 2. Tentative model of the mechanism of the goitrogenic action of cassava in iodine-deficient rats. The major step lies in the depletion of the thyroid iodine stores by a real loss of iodide.

Each of these modifications also correspond quantitatively to those observed in rats treated with 1–2 mg SCN daily.

Discussion and Conclusions

Complete similarity of the effects induced by giving either cassava or definite amounts of SCN confirm the hypothesis that the antithyroid activity of cassava is related to the endogenous production of SCN. This similarity was indeed checked qualitatively as well as quantitatively for the modifications of the SCN and the iodine metabolism.

The main effect of the prolonged consumption of cassava is a marked depletion of the iodine stores; the degree of this depletion appears strikingly severe in the absence of iodine supplementation. It is interesting to point out that the abnormalities of hormone synthesis are definitely those found in very poorly iodinated thyroglobulin (Ermans et al. 1968) or after long-term administration of low-iodine diets (Studer and Greer 1965).

Present observations moreover demonstrate that long-term consumption of cassava, as well as graded doses of SCN, induces a marked increase of the excretion rate of SCN, with the main consequence being a striking acceleration of its disposal rate from plasma. This adaptation mechanism accounts for the marked difference noticed between acute and chronic administration; it also gives an adequate explanation for the absence of inhibition of the ^{131}I thyroid uptake in the post-absorption period after chronic administration of these diets.

Two mechanisms can be advocated to explain the iodine depletion: on the one hand a transient block of iodide accumulation in the thyroid gland during the feeding period (Delange et al. 1973), and on the other hand an increase of the renal clearance of iodide. The relative importance of both factors could not be estimated on the basis of present investigations.

It seems of particular interest to mention that all abnormalities induced on the thyroid function by cassava consumption could not be distinguished qualitatively from those related to an insufficient iodine intake, with the exception of the observations specifically related to the SCN metabolism.

In conclusion, prolonged administration of cassava (or of SCN) in iodine-deficient rats provides a satisfactory model (Fig. 2) to assess the role of this foodstuff in the pathogenesis of endemic goiter.

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