

Sodium selenite enhances thyroid uptake of iodine-131 and regulates thyroid function in rats

Abstract

The aim of the present study was to evaluate the role of selenium (Se) on the thyroid uptake and retention of radioiodine (^{131}I), and on the serum levels of thyroid hormones. *Experimental rats* were divided into four groups with 10 animals in each group viz: untreated controls, ^{131}I -treated, Se-treated and ^{131}I +Se-treated. Group II and Group IV animals were injected intraperitoneally with 3.7MBq of ^{131}I . Group III and Group IV animals received Se in the form of sodium selenite, everyday at a dose of 1 ppm in drinking water. Thyroidal ^{131}I uptake measurements, determination of biological half life of ^{131}I and estimation of serum of tri-iodothyronine (T_3) and tetra-iodothyronine (T_4) and thyroid stimulating hormone (TSH) were carried out at two time intervals after 2 and 4 weeks. The statistical significance of the data was determined by using one-way analysis of variance (ANOVA) followed by Newman-Keuls test. *The results* showed lower serum levels of T_3 and T_4 and higher TSH levels in rats treated with ^{131}I when compared to untreated rats. Furthermore, the biological half life (T_{biol}) of ^{131}I in thyroid and thyroidal ^{131}I uptake values at 2h and 24h were significantly lower in rats treated with ^{131}I compared with untreated control. Selenium treatment of ^{131}I treated rats resulted in a significant increase in the thyroid uptake as well as T_{biol} of ^{131}I which indicated its increased retention. Moreover, normalization of the elevated serum TSH levels and a significant increase in the T_3 and T_4 levels was evident when Se was administered to the ^{131}I treated rats. *In conclusion*, this study indicates that Se when given to rats in the form of sodium selenite, at a dose of 1 ppm in drinking water enhances the uptake and retention of ^{131}I in the thyroid as well as regulates thyroid hormone levels.

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Introduction

A considerable part of human population suffers from thyroid abnormalities, including hyperthyroidism. The most common cause of hyperthyroidism Graves' disease while less common is toxic nodular goiter or autonomous functioning thyroid nodule. Radioiodine (^{131}I) treatment is the first line of treatment for the hyperthyroid gland and the gland becomes euthyroid due to the damage inflicted by short range beta particles emitted from the disintegrating atoms of ^{131}I , which gets accumulated within the colloids following hormogenesis [1]. However, whether patients who undergo ^{131}I treatment, will become hypothyroid after a follow-up of 1-2 years depends on the dose of ^{131}I employed [2-4]. Furthermore, if relatively low doses of ^{131}I are designed to be administered to restore euthyroidism, they may simply fail to cure the hyperthyroidism [5-7]. Therefore, studies are warranted to explore the role of drugs or metals which are non toxic and when supplemented simultaneously with ^{131}I treatment, can act as an adjunct and increase the retention of ^{131}I in thyroid follicles thereby decrease ^{131}I dose to be administered, while maintaining an euthyroid state to the patients.

It is well known that selenium (Se) plays an important role in regulating thyroid functions [8, 9]. Compared to the other parts of the body, the thyroid has the highest Se content per gram of tissue [10] and standard plasma Se concentrations range between 60 and 120 $\mu\text{g}/\text{L}$ [8]. Se is present in thyrocytes and also in follicular tissue as a co-factor of glutathione peroxidase, selenoprotein P and thioredoxin and is required for the conversion of T_4 into the more active T_3 with the help of the enzyme type 1 deiodinase [11]. Furthermore, Se in the body gets incorporated into selenoproteins which act as antioxidants and prevent the cellular damage caused by free radicals. A study by Zhong and Holmgren (2000) [12] has shown that Se is a part of the catalytic group within selenoenzymes and is directly involved in redox reactions. Experimental study on rats has also witnessed that Se administration led to a decrease of oxidative stress markers in target tissues and an increase in the level of antioxidants [13]. Therefore, the main objective of the present study was to evaluate the possible adjunctive role of Se to ^{131}I treatment by increasing the retention of ^{131}I in the thyroid gland, while maintaining a euthyroid state.

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Materials and methods

Animals

Female Sprague Dawley (S.D.) rats weighing 150 ± 20 g were procured from the central animal house, Panjab University, Chandigarh. The animals were housed in polypropylene cages in the departmental animal house under hygienic conditions as per the guidelines of the institute's ethical committee. The animals were maintained on the standard laboratory feed and water, *ad libitum*, throughout the period of experimentation.

Chemicals and equipment

All chemicals used in this study were of analytical grades. ^{131}I as a sodium iodide (carrier-free) in dilute sodium thiosulfate solution was obtained from BRIT (BARC, Mumbai, India). Sodium selenite was purchased from Loba-Chemie Indo-australian Co. The radioimmunoassay kit and immunoradiometric assay kit for the estimation of tri-iodothyronine (T_3) and tetra-iodothyronine (T_4) and thyroid stimulating hormone (TSH) were procured from BRIT (BARC, Mumbai, India).

Experimental design

Forty animals were segregated equally and randomly into 4 groups viz: Group I: Untreated controls, Group II: ^{131}I -treated, Group III: Se-treated and Group IV: Se plus ^{131}I -treated. Each group comprised of 10 rats. Animals in Groups II and IV were administered radioactivity through a single intraperitoneal (i.p) injection of 3.7MBq of ^{131}I (carrier-free) [14]. This treatment is given to irradiate thyroid gland by using therapeutic dose of ^{131}I in order to make the thyroid as hypothyroid which is a common condition that appears following ^{131}I treatment to hyperthyroid gland. Animals in Groups III and IV received Se in the form of sodium selenite in drinking water at a dose of 1ppm of Se daily [15]. Animals in Groups I and III served as untreated and Se controls, respectively. The treatment of selenium was continued for two time durations of 2 and 4 weeks. An earlier study from this lab clearly suggested that Se supplementation upto 1ppm to rats is well below the subtoxic levels and is effective in providing protection under conditions of oxidative stress [15] and therefore, the present study followed similar dosology. After the completion of the selenium treatment for two time durations, ^{131}I was administered as a tracer dose of 0.37MBq to the animals belonging to all the four groups, for the assessment of thyroidal- ^{131}I uptake and biological half life.

Thyroidal ^{131}I uptake measurements

Animals were injected intraperitoneally with 0.37MBq of carrier-free ^{131}I and thyroid uptake measurements were performed at 2h and 24h by using a well-type gamma-sensitive probe (ECIL, Hyderabad, India) [16]. For the determination of thyroidal ^{131}I uptake, rats under light ether anesthesia were held over suitably shielded gamma sensitive probe in such a way that only the neck embracing the thyroid was exposed to the probe through a hole of 1.7cm diameter in the lead shield. The lead shield (dimensions: 18.0cm x 10.5cm x 1.5cm) with a similar hole in the centre was kept over the

probe, which served the dual purpose of selectivity: a) exposing the thyroid to the probe and b) preventing the background radiation from reaching the detector. Furthermore, a glass sheet of 0.5cm thickness was placed above this shield to avoid fecal/urinary contamination of the lead shield during the uptake measurements. Moreover, the glass sheet did not allow the neck area of the animal to be pressed into the hole of the lead shield, thus maintaining the counting geometry throughout the entire uptake measurements. During the course of recording the radioactivity, three sets of measurement/counts over the thyroid were taken on each animal in order to minimize the statistical error. The standard radioactivity of ^{131}I which was equivalent to that injected to each animal was also measured, to account for the physical decay of the radioisotope during the study. Percentage uptake value of ^{131}I at 2h and 24h intervals was calculated by comparing the activity in the thyroid with that of the standard activity.

Determination of biological half-life of ^{131}I

To determine the biological half life (T_{biol}) of ^{131}I , the percentage uptake values at different time intervals were calculated with respect to counts in standard activity measured at the same time interval when the thyroid counts were actually recorded. The percent thyroid ^{131}I uptake values so determined were plotted on the Y-axis (log scale) and the time interval on the X-axis (linear scale), on the semi log paper. The values of T_{biol} of ^{131}I were interpolated from the semilog plot and were calculated by taking the difference on the X-axis of any two points, where the percentage uptake was bisected.

Estimation of serum T_3 , T_4 and TSH

Animals were anaesthetized using mild ether anesthesia and blood samples were drawn from the ocular vein, (retro-orbital plexus). Serum was separated by centrifugation and stored at -20°C . Serum concentrations of total T_3 and thyroxine T_4 were determined by using radioimmunoassay kit (BRIT, India) and of TSH concentrations by using immunoradiometric assay kit procured from BRIT, (India).

Statistical analyses

The statistical significance of the data was determined by using one-way analysis of variance (ANOVA) followed by Newman-Keuls test. The results are presented as means \pm SD.

Results

Results obtained from the above experiments are depicted in Tables 1-3. Additionally, results obtained from the ^{131}I +Se treated group were additionally compared with the ^{131}I treated group.

Thyroidal ^{131}I uptake and the T_{biol} of ^{131}I

Thyroidal ^{131}I uptake values at 2h and 24h were found to be significantly lower 2 and 4 weeks when compared to untreated controls. However, they were significantly higher upon Se supplementation and did not differ from the control group (Table 1).

The biological half life of ^{131}I after 4 weeks was not statistically significantly lower in the ^{131}I treated group of rats in

comparison to group I animals (Table 2). Furthermore, co-administration of Se to ^{131}I treated rats showed a significant increase in T_{biol} of ^{131}I both at 2h and at 24h when compared to the ^{131}I -treated group. A significant increase in T_{biol} of ^{131}I was also witnessed in rats that were given Se alone for 4 weeks when compared to normal control group.

T₃, T₄ and TSH levels

The levels of total T₃, T₄ and TSH in serum of rats belonging to normal and treated groups at time intervals of 2 and 4 weeks are presented in Table 3. A statistically significantly lower in the levels of T₃ and T₄ with a concomitant higher TSH levels were observed following ^{131}I treatment when compared with the untreated control. However, simultaneous administration of Se to ^{131}I treated rats resulted in a significantly higher levels of T₃ and T₄ with a concomitant decrease in the levels of TSH when compared with the ^{131}I -treated group. Furthermore, the levels of T₄ and TSH in the combined Se and ^{131}I treated group returned within normal limits.

Discussion

The decreased thyroidal ^{131}I uptake following ^{131}I treatment is attributed to the reduced trapping efficiency of thyroid follicles for inorganic iodide as a result of damage inflicted by beta particles emitted from the disintegrating radioactive atoms of ^{131}I , localized within the thyroid follicles. However, Se administration to ^{131}I -treated rats resulted in a significant increase in the 2h and 24h thyroidal ^{131}I uptake at both time intervals when compared with ^{131}I -treated rats, which is most likely due to the antioxidative potential of Se that plays an important role in repairing and maintaining the integrity of thyroid follicles [17, 12]. Iodine-131 treatment of rats did result in some decrease in T_{biol} of ^{131}I , 2 and 4 weeks after treat-

ment which was not statistically significant and could be attributed to the recovery of the damaged thyroid follicles in the course of time, as the entire gland was not ablated by the ^{131}I . However, Se supplementation of ^{131}I -treated rats significantly increased the T_{biol} of ^{131}I thereby indicating its increased retention in the thyroid follicles which apparently is due to blockade of ^{131}I release from the thyroid into the circulation. Furthermore, we have also observed an expected decrease in the levels of serum T₃ and T₄ which is understandable in the light of damage caused by ^{131}I beta particles on follicles in the thyroid gland [16]. Also, there are various reports that have highlighted the decrease in the levels of circulating thyroid hormones both in human and animals following ^{131}I treatment [18-20].

Accordingly, levels of TSH increased following ^{131}I treatment. This increase in TSH levels following ^{131}I treatment had also been reported by Guajardo-Salinas et al (2007) [21] and from our laboratory, as well [16]. High TSH levels thus stimulate thyroid tissue to increase ^{131}I uptake and also stimulate the secretion of thyroglobulin [22]. Hence, the effectiveness of ^{131}I treatment for thyroid carcinoma depends on serum TSH being sufficiently elevated which is believed to increase sodium iodide symporter (NIS) expression and thereby optimizes ^{131}I uptake [23]. Furthermore, Se supplementation was able to restore both T₄ and T₃ levels to the normal limits, possibly by upregulation of peroxidase activity for which selenium acts as a cofactor. Similar effect of Se supplementation has also been observed in another study where rats fed with diets containing 1ppm selenium were reported to have elevated T₃ and T₄ concentrations in serum [24]. Levels of T₃ were not restored to normal limits after 2 weeks, which could be attributed to its utilization in the body as the primary working hormone in contrast to T₄. However on continued supplementation with selenium for 4 weeks there was an increase in T₃ levels, as well. This effect could possibly be due to increased formation of T₃ from T₄

Table 1. Effect of selenium on the thyroidal ^{131}I % uptake at 2h and 24h in different treatment groups % uptake of the administered dose

Groups	2 weeks		4 weeks	
	2h	24h	2h	24h
Untreated control	34.2±4.1	54±8.4	32.4±4.2	51.1±5.7
^{131}I treated	27.9±2.2 ^a	33.2±3.2 ^c	27.6±2.4 ^a	30.6±4.1 ^b
Se treated	35.6±3.5	47.2±4.4	30±4.4	42.8±8.4
^{131}I +Se treated	36.4±4.2 ^y	44.0±4.8 ^z	34.2±1.7 ^x	39.1±5.5 ^{a,x}

All data are expressed as mean ±SD. ^aP<0.05, ^bP<0.01 and ^cP<0.001 by Newman-Keuls test when values are compared with the control Group. ^xP<0.05 and ^yP<0.01 by Newman-Keuls test when values of Group IV are compared with Group II.

Table 2. Biological half life of ^{131}I in different treatment groups

Groups	2 weeks	4 weeks
	(Days)	(Days)
Untreated control	3.6±0.2	3.3±0.5
^{131}I treated	3.3±0.5	2.8±0.4
Se treated	3.8±0.4	4.3±0.4 ^a
^{131}I +Se treated	4.4±0.4 ^{b,y}	4.8±0.8 ^b

All data are expressed as mean±SD. ^aP<0.05, ^bP<0.01 and ^cP<0.001 by Newman-Keuls test when values are compared with the control Group. ^xP<0.05 and ^yP<0.01 by Newman-Keuls test when values of Group IV are compared with Group II.

Table 3. Effect of Se on T₃, T₄ and TSH levels in the serum of ¹³¹I treated rats

Groups	T ₃	T ₃	T ₄	T ₄	TSH	TSH
	(2weeks)	(4weeks)	(2weeks)	(4weeks)	(2weeks)	(4weeks)
Untreated control	1.56±0.57	1.1±0.06	9.3±0.39	8.8±0.44	0.63±0.15	0.62±0.13
¹³¹ I treated	0.68±0.11 ^c	0.69±0.33 ^c	7.9±0.43 ^a	7.0±0.59 ^a	1.1±0.30 ^a	1.1±0.15 ^b
Se treated	1.83±0.13	1.29±0.18	10.4±1.70	9.4±1.51	0.83±0.31	1.25±0.13 ^c
¹³¹ I+Se treated	0.89±0.10 ^{b,x}	0.97±0.35 ^{a,x}	9.0±0.54 ^x	10.05±1.41 ^y	0.78±0.32 ^x	0.84±0.15 ^y

T₃ expressed in ng/ml of serum, T₄ expressed in µg/dL of serum, TSH expressed in µIU/mL of serum. All data are expressed as mean±SD. ^aP<0.05, ^bP<0.01 and ^cP<0.001 by Newman-Keuls test when values are compared with the control group.

^xP<0.05 and ^yP<0.01 by Newman-Keuls test when values of Group IV are compared with Group II.

with the support of Se containing enzyme iodothyronine 5'-deiodinase. Similar increase in T₄ levels has been also observed in another study, where the supplementation of Se to cadmium (Cd) exposed rats, has been found to protect from Cd induced decrease in serum T₄ levels [25]. This clearly emphasizes the selenium serves the triple purpose element, as on one side it increase the retention of ¹³¹I thereby giving a certain possibility of decreasing the therapeutic dose of ¹³¹I during the treatment of hyperthyroidism, secondly it may regulate thyroid hormones by increasing the chances of maintaining euthyroid state following treatment of hyperthyroidism and thirdly helping in performing various other organ functions because of being an essential element.

In conclusion, the present study reports that simultaneous supplementation of Se with ¹³¹I treatment shall enhance the uptake and retention of ¹³¹I in the thyroid as well as regulate thyroid hormones levels. Therefore, Se has the potential to be used as an adjunct to ¹³¹I treatment and to overcome the possibility of hypothyroidism following ¹³¹I treatment in hyperthyroid patients. However, further confirmative studies on the functional regulation of thyroid by Se and on its mechanism of action at the molecular level are required.

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The authors declare that they have no conflicts of interest.

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