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Biological Half-Life of Bromine in the Rat Thyroid

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Summary

The biological half-life of bromine in the rat thyroid was determined by measuring the radioactivity of thyroids of animals which continuously received ^{82}Br labelled bromide in their food. The value of this half-life (110 h) is practically the same as the biological half-life of iodine. The rate of establishing the I/Br concentration ratio in the thyroid depends on the biological half-life of bromine. The mechanism of this process depends on the state of iodine supply. When the supply is sufficient, the iodine concentration in the thyroid remains constant, while during iodine deficiency the iodine atoms are replaced by atoms of bromine.

Key words
Bromine – Biological half-life – Rat – Thyroid – I/Br ratio

Introduction

In previous experiments, in which we followed the effect of increasing bromide intake on iodine excretion in rats, we also determined the biological half-life of bromine (Vobecký *et al.* 1996a). However, the value of 13.5 days did not correspond to the results of our other experiments in which a stable I/Br concentration ratio in the rat thyroid was attained as early as 15 days after bromide administration (Vobecký and Babický 1994). In case that the biological half-life of bromine in the rat thyroid was of the same value, i.e. 13.5 days, then the biological half-life of iodine would have to be much shorter than 106 hours in order to reach a stable I/Br concentration ratio in such a short time. As was shown in our preceding paper, however, even a strong increase in bromide intake failed to affect the rate of iodine excretion (Vobecký *et al.* 1996a). This discrepancy could be explained by assuming that the biological half-life of bromine in the rat thyroid is shorter than the whole-body half-life, and that it is most probably close to that of iodine. This different half-life, however, did not affect the rate of bromine excretion because only a negligible amount of administered bromide, including the radioactive tracer, had been accumulated in the thyroid.

It is known that, by repeated administration, the steady concentration of a substance can be attained in the target organ, and that this concentration is directly proportional to the biological half-life of this substance (Rauws 1975). We decided therefore to determine the biological half-life of bromine in the rat thyroid by measuring the radioactivity of thyroid samples collected from animals which had free access to drinking water containing the bromide labelled by the radionuclide ^{82}Br. Furthermore, by measuring the iodine and bromine concentration in the thyroid, we were also able to determine the rate of establishing the I/Br concentration ratio.

Methods

The experiments were performed on 35 male Wistar rats two and half months old (285±12 g mean body weight). The animals were divided into 7 equal-sized groups and were fed *ad libitum* with pellet diet (supplied by Bergman, Kocanda near Prague) with a mean bromine concentration of 4.2 μg/g. The bromine concentration in the diet was determined by the method of instrumental neutron activation analysis (INAA), that of iodine by the method of kinetic photometry. During the pre-experimental period of 10 days, the rats

drank distilled water *ad libitum* while during the experimental 16-day period all animals drank distilled water containing 1 μg/g of iodide (KI) and 100 μg/g of bromide (NaBr) labelled by the radionuclide ^{82}Br. The radionuclide ^{82}Br was prepared by irradiating the KBr target with neutrons in the core of the LWR-15 nuclear reactor (Nuclear Research Institute, Řež near Prague) for 10 h at 8 MW output. At the start of the experiment, the volume radioactivity of the drinking water offered to the first five groups was 20.9 kBq of ^{82}Br per ml. Due to the short half-life of ^{82}Br (35.3 h), the drinking water supplied to the last two groups had five times higher volume radioactivity. The water and diet consumption was followed daily.

The animals were killed under light ether narcosis at the appropriate time intervals by carefully cutting their jugular veins. Then thyroids were collected and their radioactivity was measured by a gamma counter MINAXI 5000 (Packard). After decay of ^{82}Br radioactivity, the thyroids of each group were pooled, dried and their bromine and iodine concentration was determined by INAA (Vobecký and Babický 1994). The time course of the changes in the radioactivity concentration of the samples, neglecting the radioactive decay of ^{82}Br, was calculated according to the following equation:

$$[Br]_t = A \times \{1 - [\exp -(0.693/T_b) \times t]\}, \quad (1)$$

where $[Br]_t$ is the radioactivity concentration of ^{82}Br in the rat thyroid, given in cpm/g wet weight (w.w.) at time t, A is the steady state radioactivity concentration which can be attained in the thyroid under the given experimental conditions, expressed in cpm/g w.w., T_b is the value of searched biological half-life of bromine in the rat thyroid, given in hours, and t is the time which elapsed from the moment at which the drinking water was offered to the animals for the first time, given in hours. The value of A was extrapolated from the time course of experimentally found values. The value of T_b was obtained by fitting a curve to these values using the method of least squares.

For calculating the actual radioactivity concentration values, it is necessary to multiply Eq. (1) by a correction factor which expresses the magnitude of the ^{82}Br non-disintegrated fraction at the given time:

$$[Br]_{ta} = f \times [Br]_t, \quad (2)$$

where $[Br]_{ta}$ is the actual radioactivity concentration of ^{82}Br in the thyroid, expressed in cpm/g w.w., f is the correction factor which states the magnitude of non-disintegrated ^{82}Br fraction:

$$f = \exp[-(0.693/T_{ph}) \times t] \quad (3)$$

T_{ph} is the value of the half-life of ^{82}Br radioactive decay given in hours (i.e., 35.3).

The rate of I/Br molar concentration ratio established in the thyroid was calculated according to the following equations:

$$[R]_t = [I]/[Br]_t, \text{ and} \quad (4)$$
$$[R]_t = ([I]/[Br]_t) - 1, \quad (5)$$

where $[R]_t$ is the rate of I/Br ratio establishing, [I] is the iodine concentration in the thyroid, given in μmol/g dry weight (d.w.), and $[Br]_t$ is the bromine concentration in the thyroid, given in μmol/g d.w.

Equation (4) was calculated on the assumption that the iodine concentration in the thyroid remains constant. Equation (5) was calculated on the assumption that in the course of this process the iodine atoms in the thyroid were replaced by bromine atoms.

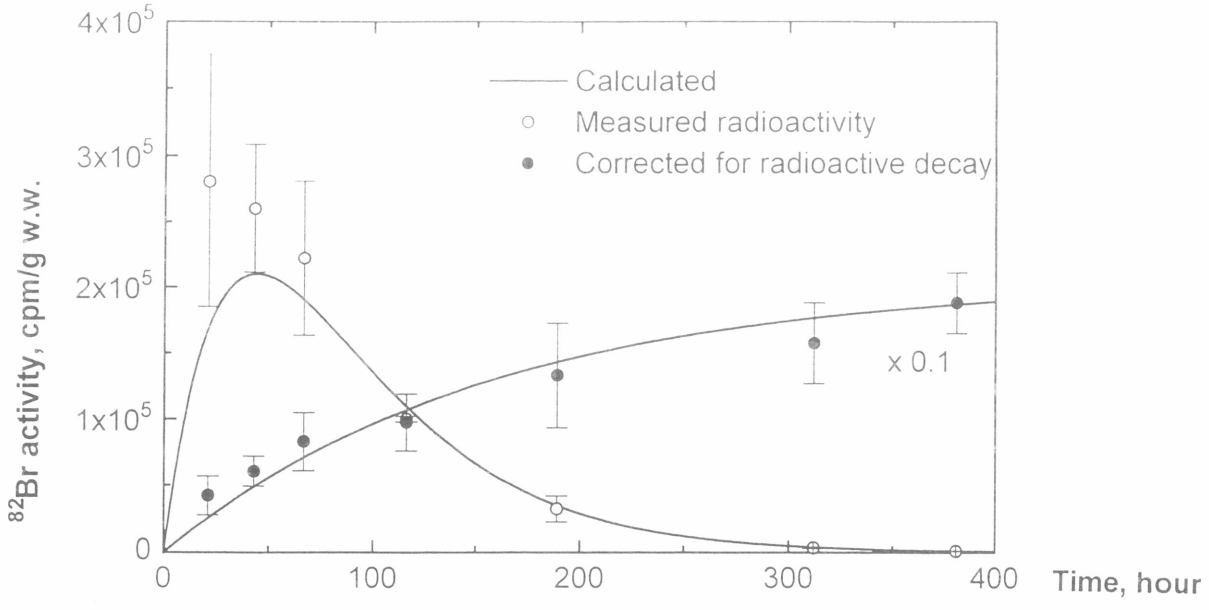

Fig. 1. *^{82}Br activity of the thyroid gland, expressed in cpm per g of wet weight, in dependence on the duration of labelled bromide intake. The results are given as the arithmetical mean ± S.D. (n = 5). Values corrected for radioactive decay (full circles) were reduced by a factor of 10 in relation to the activity scale.*

Results

The mean daily consumption of drinking water per animal was 33.2 ml, and that of the diet was 22.3 g, which represents the mean intake of 35.4 μg of iodine and 3414 μg of bromine per animal per day. At the beginning of the experiment, especially on the first day, the consumption of water was higher than the mean value, in some cases by even more than several tens of per cent. The mean weight of thyroid glands of the rats used in this investigation was 11.2±1.8 mg and did not change significantly in the course of the experiment.

The results of the radioactivity measurements in the thyroids are shown in Fig. 1. The extrapolated value of the steady-state radioactivity concentration equals $A = 2.058 \times 10^6$ cpm/g w.w. Both the radioactivity and mass concentrations of bromine at time t=0 were negligible, so it was possible, on the basis of known bromine specific radioactivity in drinking water, to express the radioactivity concentration also in terms of mass concentration. The extrapolated value of bromine steady state concentration expressed in this way equals A=0.175 mg Br/g w.w. When taking into account that the dry weight of the rat thyroid is 27.2 % of the wet weight on the average, the value of the parameter A expressed in mg Br/g dry weight is 0.643. The value of biological half-life of bromine in the rat thyroid obtained by fitting a curve to the results of the radioactivity measurement is T_b = 110 hours.

Table 1
Concentrations of bromine and iodine in the thyroid gland

Bromide exposure (h)	Element concentration (μg/g dry weight)		
	Determined by INAA		Calculated from ^{82}Br specific activity
	I	Br	Br
21	1312	163	132
43	2652	225	189
67	2369	259	259
116	2918	276	304
189	1933	425	416
312	2374	438	493
381	2003	440	590
Mean	2223		

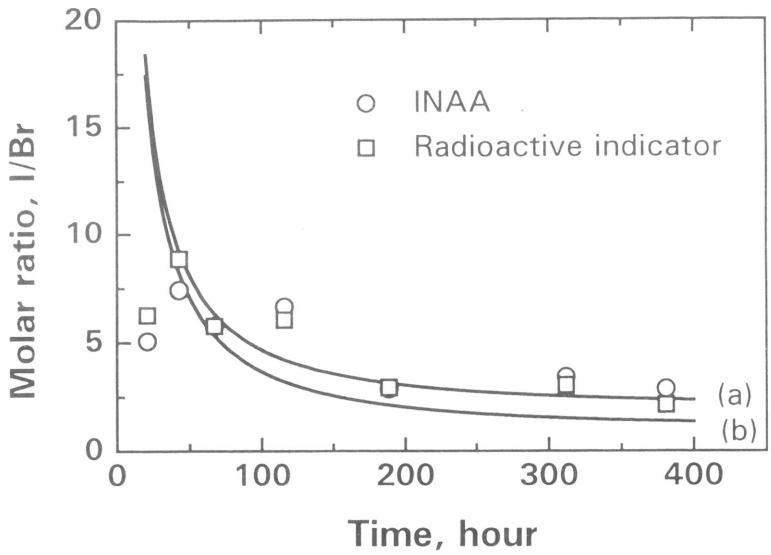

Fig. 2. *Time course of establishing the I/Br molar ratio: curve (a) according to Eq. (4), curve (b) according to Eq. (5).*

The bromine and iodine concentrations in the thyroid determined by the INAA method, and in case of bromine also calculated on the ground of Eq. (1), are summarized in Table 1. The rate of I/Br molar concentration ratio occurring in the thyroid is illustrated in Figure 2. The theoretical course of this process is shown in this figure by curves (a) and (b), calculated according to Eq. (4) and (5).

Discussion

It is evident from Fig. 1 that the calculated equations agree well with the experimentally found values of radioactivity concentrations. Somewhat greater differences at the beginning of the experiment are primarily due to the fact that it was not possible to specify exactly time t = 0. Furthermore, the consumption of drinking water, and consequently the intake of radioactive bromide, was greater at the beginning than the mean intake which could be connected with changes in the composition of the drinking water.

The found value of the biological half-life of bromine in the rat thyroid (110 h) fully confirmed our hypothesis that this half-life is close to the value of biological half-life of iodine (106 h) published recently by Singh *et al.* (1994). The fact that both half-lives are identical can be considered as further proof that, in contrast to other organs, the biological behaviour of bromine in the thyroid is not similar to the biological behaviour of chlorine but resembles more that of iodine (Vobecký *et al.* 1996b).

With the exception of the last two values, Table 1 shows that the values of bromine concentration in the thyroid calculated from the radioactivity data and those determined by INAA are in good agreement. The calculated value for the 16th day of the experiment (7.38 μmol/g d.w.) also compares well with the results of our preceding experiment. Under analogous experimental conditions, the bromine concentration in the thyroid, determined by INAA, was 7.37 μmol/g d.w. (Vobecký and Babický 1994).

At present, we are not able to explain unequivocally the rather large scatter of the iodine concentration values, especially at the beginning of the experiment. Since we can exclude with a high probability any occurrence of experimental errors, we assume that a sudden change in the ratio of iodide to bromide in the food could cause initially an inadequate reaction of the thyroid. The course of this reaction, however, resembles the course of changes in the iodine content in the thyroid of rats injected with high doses of KI (Wolff and Chaikoff 1948). Further experiments should show whether plasma inorganic bromide could in some way also act as iodide.

It is evident that the I/Br concentration ratio in the thyroid very promptly reflects the increase in bromide intake. The most rapid drop of this ratio occurred during the first four days of enhanced bromide intake. With the exception of the first value, owing to the extremely low value of iodine concentrations, the other experimentally found values are in a good agreement with the calculated ones. The I/Br concentration ratio at time zero could not be estimated, in principle, by measuring radioactivity of the ^{82}Br indicator in the thyroid. However, the iodine and bromine concentrations at time t = 0, immediately before the start of the experiment, could be determined by INAA. In fact, we performed similar experiments under analogous conditions previously and found, by using INAA, the following concentrations in the dried thyroid glands: [I] = 19.50 μmol/g d.w., $[Br]_{t=0}$ = 0.34 μmol/g d.w., and corresponding molar concentration ratio I/Br = 56.5 (Vobecký and Babický 1994) and [I] = 15.30 μmol/g d.w., $[Br]_{t=0}$ = 0.19 μmol/g d.w., and I/Br = 80.5, respectively (Vobecký *et al.* 1997).

The time course of the changes indicates that the I/Br ratio progressed according to Eq. (4). We suppose that the decisive role in establishing this ratio is played by the state of iodine supplementation. The results of our other experiments, in which we followed the influence of increasing bromide intake on the I/Br ratio and on the iodine concentration in the thyroid under conditions of various iodide supplementation, also confirm this conclusion. We found that the I/Br ratio in the thyroid dropped very rapidly in rats fed a diet containing 0.1 μg/g of iodine. This iodine concentration represents only 2/3 of the recommended dose which is guaranteed by a diet for rats with iodine concentration of 1.2 μmol/kg (Jansen *et al.* 1994). The iodine concentration in the thyroid remained stable and also the drop in the I/Br ratio was much slower in rats fed surplus iodide (Vobecký *et al.* 1997). These findings are in a good correspondence with the statement of Buchberger *et al.* (1990) that bromine toxicity is dependent upon the state of the iodine supply.

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Reprint requests

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