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Metabolism of Bromide and Its Interference with the Metabolism of Iodine

S. PAVELKA

Department of Radiometry, Institute of Physiology, Academy of Sciences of the Czech Republic, Prague and Department of Biochemistry, Faculty of Science, Masaryk University, Brno, Czech Republic

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Summary

The present knowledge about the metabolism of bromide with respect to its goitrogenic effects, including some conclusions drawn from our recent research on this subject, is reviewed. Firstly, the biological behavior of bromide ion is compared with that of chloride and iodide. Secondly, the details about distribution and kinetics of bromide ions in the body and in 15 different organs and tissues of the rat are given. Significant correlation between the values of the steady-state concentration of bromide in the respective tissue and of the corresponding biological half-life was found in most tissues examined. A remarkably high concentration of radiobromide was found in the skin, which represents, due to its large mass, the most abundant depot of bromide in the body of the rat. Thirdly, the effects of excessive bromide on the rat thyroid are summarized, along with the interference of exogenous bromide with the whole-body metabolism of iodine. It is suggested that high levels of bromide in the organism of experimental animals can influence their iodine metabolism in two parallel ways: by a decrease in iodide accumulation in the thyroid and skin (and in the mammary glands in lactating dams), and by a rise in iodide excretion by kidneys. By accelerating the renal excretion of iodide, excessive bromide can also influence the pool of exchangeable iodide in the thyroid. Finally, our recent results concerning the influence of high bromide intake in the lactating rat dam on iodine and bromide transfer to the suckling, and the impact of seriously decreased iodine content and increased bromide concentration in mother's milk on the young are discussed. We must state, however, that the virtue of the toxic effects of excessive bromide on the thyroid gland and its interference with the biosynthesis of thyroid hormones, as well as the exact mechanism of bromide interference with postnatal developmental processes remains to be elucidated.

Key words
Bromide • Iodide • Metabolism • Rat • Thyroid

Introduction

Bromine is one of the most abundant and ubiquitous of the recognized trace elements in the biosphere. However, bromine has not been conclusively shown to perform any essential function in plants, microorganisms or animals (Pavelka 2004). In nature, bromine is found mostly bound to metals in the form of inorganic salts – the bromides. Bromide is the main degradation product of brominated hydrocarbons (e.g.

Fax +420 241 062 164
E-mail: physres@biomed.cas.cz
http://www.biomed.cas.cz/physiolres

methyl bromide) excessively used in agriculture for pre-planting fumigation of soils and post-harvest fumigation of commodities as grains, spices, nuts, fruits and tobacco; as well as of other bromine compounds (e.g. ethylene dibromide) applied on a large scale in industry. In the course of the 20th century bromide has been introduced increasingly into the environment as a salt-mining waste and a degradation product of fumigants. Therefore, at present the general population will mainly be exposed to bromide *via* their food. The new role of bromide as a residue in food and water necessitated its broad toxicological evaluation (Van Leeuwen and Sangster 1987).

The present knowledge about the metabolism of bromide with respect to its goitrogenic effects, including some conclusions following from the results of our recent research on this subject, is reviewed in this brief survey. Since inorganic bromide is the ionic form of bromine exerting the therapeutic as well as the toxic effects, mainly studies dealing with the exposure to bromide will form the basis of this review.

Comparison of the metabolism of bromide with that of chloride and iodide

Not enough information is available on bromine metabolism; the element appears to be well absorbed and is mostly excreted in the urine, whether ingested or injected (Cole and Patrick 1958, Hellerstein *et al.* 1960). No organisms other than marine sponges and gorgonians incorporate bromine into organic compounds (such as bromotyrosines in the scleroproteins of support tissue). Hence, bromine metabolism in most living organisms is that of the bromide ion. Species differences in tissue bromine concentrations are small and the element does not accumulate to any marked degree in any particular organ or tissue (Cole and Patrick 1958, Hellerstein *et al.* 1960, Hamilton *et al.* 1972/1973). Earlier claims that bromine is concentrated in the thyroid and pituitary glands (Dixon 1935, Baumann *et al.* 1941, Perlman *et al.* 1941) have not been substantiated (Söremark 1960a, Ullberg *et al.* 1964, Pavelka *et al.* 2000b), with the possible exception of the hyperplastic thyroid (Baumann *et al.* 1941).

There is no evidence in humans of bromide concentration in any particular organ that might indicate a specific physiological function of this ion. After oral ingestion, bromide is rapidly and completely absorbed in the gastrointestinal tract and, analogously to chloride, distributed almost exclusively in the extracellular fluid (with the exception of erythrocytes). Mason (1936) had already recognized that bromide replaces part of the extracellular chloride, the molar sum of chloride and bromide remaining constant at about 110 mmol/l. The similarity of bromide to chloride entails an important pharmacokinetic interaction; both ions compete for tubular reabsorption (Rauws 1983). The biological half-life of bromide can be decreased by administering surplus chloride ions (Langley Czerwinski 1958). On the contrary, the already long half-life of bromide, which is about 12 days in humans (Söremark 1960b) and approximately 3 to 8 days in the rat (Rauws and Van Logten 1975, Pavelka *et al.* 2000a), may be increased considerably by a salt-deficient diet (up to 25 days in the rat on a salt-free diet – Rauws and Van Logten (1975)). Considering the chemical similarity of bromine to iodine, on the other hand, goitrogenic effects of bromide may be assumed. Indeed, an enhanced bromide intake in the rat could markedly reduce iodide accumulation in the thyroid (Van Leeuwen *et al.* 1988, Buchberger *et al.* 1990, Pavelka *et al.* 1999a), as well as in the skin (Pavelka *et al.* 2001b).

Iodine deficiency disorders and the goitrogenic effects of bromide

It is estimated that there are about 1.6 billion people on our planet whose average iodine intake is insufficient (Delange 1995) and who are, therefore, at risk of health problems connected with iodine deficiency (Hetzel 1983). These include about 650 million people afflicted by goiter. Health problems connected with a deficit of iodine intake, including abnormal functions of the thyroid, are still relevant in a number of European countries including the Czech Republic (Delange 1995). Apart from the severity degree of iodine deficiency, the symptomatology and frequency of iodine deficiency disorders are also influenced by other goitrogenic factors and trace elements. Besides the known goitrogens of plant origin, increasing importance is also given to goitrogenic agents of anthropogenic origin of both organic and inorganic character, especially in connection with the increasing contamination of the environment. Above all bromine, because of its chemical similarity to iodine, belongs among these goitrogens. The study of goitrogenic effects of bromine compounds becomes particularly significant in circumstances of a moderate iodine deficiency when they can interfere with the production of thyroid hormones (Buchberger *et al.* 1990).

There is a general assumption that the biological behavior of bromine is similar to chlorine so that administration of bromide results in some displacement

of body chloride and *vice versa* (Hellerstein *et al.,* 1960). This is not obviously valid for the thyroid gland. In the studies on the interaction of bromine with iodine in the rat thyroid under the conditions of enhanced bromide intake we found that in this tissue, contrary to other tissues, bromide did not replace chloride but rather iodide (Pavelka *et al.* 1999a, Vobecký *et al.* 2000). Until recently, studies following the effects of enhanced supply of bromide into the organism of experimental animals were carried out mostly on adult individuals and at normal iodine availability. Van Leeuwen *et al.* (1983) and Loeber *et al.* (1983) were among the first who proved the toxic effect of high bromide doses on the morphology and function of the thyroid. Later Van Leeuwen *et al.* (1988) stated that bromide affected the thyroid peroxidase activity. However, this hypothesis was disproved by Taurog and Dorris (1991), who observed that even a 200-fold excess of bromide in comparison with iodide in an *in vitro* incubation system had no effect on the rate of thyroid peroxidase-catalyzed iodination of thyroglobulin. In addition, they concluded that even large doses of bromide did not interfere with iodide transport into the thyroid. Buchberger *et al*. (1990) studied the effects of chronic administration of large bromide doses on the biosynthesis of thyroid hormones in iodine-deficient rats. The results of this study indicate that bromide toxicity is dependent upon the state of iodine supply in the organism: the signs of hypothyroidism caused by bromide intake were significantly enhanced under the conditions of simultaneous iodine deficiency. The virtue of the toxic effects of bromide on the thyroid gland and mechnisms of its interference with the biosynthesis of thyroid hormones, however, have not been so far elucidated.

Distribution and kinetics of bromide ions in the body

The distribution and kinetics of bromide in the body of various animals and humans have been investigated by several authors using chemical analytical methods (Mason 1936, Hellerstein *et al.* 1960) as well as isotope techniques involving ^{82}Br (Cole and Patrick 1958, Söremark 1960a, Ullberg *et al.* 1964). Except for the central nervous system, bromide has been found to pass rapidly into various tissues and mainly into the extracellular fluid of the body. Bromide has also been found to be partitioned in the body similarly to chloride (Ullberg *et al.* 1964), so that under the conditions of enhanced intake, bromide replaces chloride throughout the tissues and fluids of the body. Söremark (1960a) performed a detailed study of bromide distribution in mice, rats and rabbits. The distribution was followed after injection of bromide labeled with the radionuclide ^{82}Br (with the physical half-life of radioactive decay of only 35.3 h) both by autoradiography and by measuring radioactive concentration of labeled bromide in various organs of experimental animals. However, these observations were limited only to the period of 72 h after injection and the results of radioactive concentration measurements were given merely as the ratios of radioactive concentration of ^{82}Br in a sample to the radioactive concentration in the blood.

Since the previous studies, which had used tracer methods were limited by technical feasibilities at that time, we decided to investigate in more detail the bromide distribution in rats by means of more sophisticated methods. The use of a semiconductor detector allowing more sensitive measurement of samples of greater volume, including living animals, on the one hand, and the oral administration of labeled bromide (in addition to injection), on the other, enabled us to extend markedly the period of observation, to express the amount of bromide retained in the individual organs as well as in the whole body, and to make a total bromide balance (Pavelka *et al.* 2000a,b). The distribution of ^{82}Br-bromide in 15 different organs and tissues of rats has been determined by high-resolution gamma-ray spectrometry and by scintillation counting technique at different times after the application of Na^{82}Br, either by subcutaneous injection or by continuous administration in the drinking water. The amount of ^{82}Br-bromide in various tissues reached its largest uptake within a few hours, and the concentration ratio of ^{82}Br in the tissues to blood remained practically constant between 8 h and 396 h after the application. The whole stomach was the only organ in the rat, which had a larger uptake of ^{82}Br than blood. Contrary to some previous findings mentioned in the literature, the concentration of radiobromide in the thyroid was not found to exceed that in the blood. A remarkably high concentration of ^{82}Br was found in the skin that represented, due to its large mass, the most abundant depot of bromide in the body of the rat (Pavelka *et al.* 2000b).

The demonstrated excretion of bromide was mainly renal, at a rate of approximately 5 % of the administered dose per 24 h. In addition to the whole-body half-life, we have determined biological half-life values of bromide in 15 different organs and tissues of the rat by measuring the radioactive concentration of ^{82}Br-bromide in samples of tissues collected at the time intervals of 12-396 h from animals which received ^{82}Br-labeled

bromide in their drinking water continuously (up to 17 days) (Fig. 1). The half-life values ranged from about 94 h in the thyroid gland to 235 h in the liver and in most of the studied tissues the values were shorter than in the whole body, in which it equaled about 198 h. Significant correlation between the values of the steady-state concentration of bromide in the respective tissue and of the corresponding biological half-life was found in most tissues examined (Pavelka *et al.* 2000a).

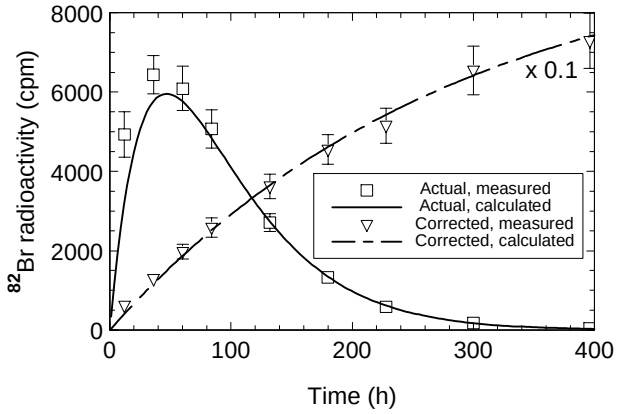

Fig. 1. Time-course (□ actual, and ▼ corrected for the radioactive decay of ^{82}Br) of the accumulation of ^{82}Br-bromide in the body of rats (n = 5) during continuous administration of Na ^{82}Br in drinking water. [Modified from Pavelka *et al.* (2000a)].

Effects of excessive bromide on the rat thyroid

A remarkable complex of presumably related changes in the endocrine system induced by bromide was observed in male rats fed a very high dose of sodium bromide in the diet (19.2 g NaBr per kilogram diet) for 4 or 12 weeks (Van Leeuwen *et al.* 1983, Loeber *et al.* 1983). The most striking effects of bromide on the endocrine system were found on the thyroid gland and the gonads. Activation of the thyroid, characterized by an increase in relative weight of the organ and a reduction in follicle size, was observed (Loeber *et al.* 1983). These phenomena were accompanied by a decrease in serum thyroxine (T_4), indicating a typical hypothyroidism induced by bromide (Loeber *et al.* 1983, Pavelka *et al.* 2002).

In studies on the interference of exogenous bromide with iodine metabolism in the rat tissues we have found that under the conditions of increasing bromide intake the thyroid responded very sensitively to even relatively small increase in bromide intake (e.g. approximately 0.4-4 mg Br^- per day, received in drinking water supplemented with 0.01-0.1 g bromide per liter) by a marked decrease of the [I]/[Br] concentration ratio (Vobecký *et al.* 1997b). A stable value of this ratio was established during approximately 15 days of administration of a diet with bromide supplementation. It is important that the magnitude of the decrease in the [I]/[Br] ratio also depended on the level of iodine supply in the organism. The [I]/[Br] ratio in the thyroid was as much as five times lower in rats with a marginal iodine deficiency than in animals with a sufficient or an excessive iodine intake. On the other hand, superfluous iodine intake had no effect.

With the aid of the short-term instrumental neutron activation analysis of the isolated lyophilized rat thyroids we found that at enhanced bromide intake, bromine in the thyroid did not replace chlorine, like in all other tissues, but iodine (Vobecký *et al.* 2000). Under our experimental conditions up to 40 % of the amount of iodine in the thyroid was replaced by bromine. Most probably, bromine in the thyroid remains in the form of bromide ion and, in proportion to its increasing concentration, the production of iodinated thyronines decreases. The analyses of fractionated thyroids showed that the most pronounced decrease in the [I]/[Br] ratio occurred in the soluble low-molecular weight fraction, containing mostly inorganic ions and possibly free halogenated aminoacids. In the high-molecular weight soluble fraction of the thyroid, containing thyroglobulin with covalently bound halogenated residues of tyrosine and thyronines, even a high bromide intake did not displace organically bound iodine so that the [I]/[Br] ratio changed only slightly. These results indicate that with sufficient iodine supply in the organism, a stable [I]/[Br] concentration ratio in the thyroid is rapidly established during the exposure of rats to increased concentrations of bromide, while under iodine deficiency iodine atoms in the thyroid are replaced by bromine atoms.

Using radionuclides ^{82}Br and ^{131}I and whole-body measurement of the retained activity, we found that the time course of bromine excretion in adult male rats substantially differed from iodine excretion (Pavelka *et al.* 1998). The whole-body excretion curve of bromine showed only a single rate constant with a biological half-life longer than 10 days. In contrast, iodine was apparently excreted from two different pools: the first with a very short half-life (less than 12 h), characterizing the clearance of excess iodine from the organism; and the second with a half-life of about 108 h, accounting for

iodine release from the thyroid. The rapidity of the attainment of a stable [I]/[Br] concentration ratio in the thyroid implicated that the biological half-life of bromine in the rat thyroid was substantially shorter than the whole-body one, and that it was probably close to the half-life of iodine. This different half-life of bromine, 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 have used this principle for the determination of the biological half-life of bromine in the rat thyroid by measuring the radioactivity of isolated thyroids of animals which continuously (during 16-day experimental period) received ^{82}Br-labeled bromide in their diet (Vobecký *et al.* 1997a). The found value of this half-life (about 110 h) was very close to the measured value of the biological half-life of iodine (about 108 h) and to the value (106 h) published recently for iodine by Singh *et al.* (1994). The fact that the values of the half-lives of bromine and iodine in the rat thyroid are practically identical can be considered as further proof that the biological behavior of bromine in the thyroid, in contrast with other organs, is not similar to the biological behavior of chlorine but resembles more that of iodine.

Interaction of bromide with iodide uptake by the thyroid gland most probably is the underlying mechanism leading to thyroid dysfunction and consequently to the observed alterations in the pituitary-thyroid axis (Loeber *et al.* 1983, Van Leeuwen *et al.* 1983, 1988, Pavelka *et al.* 2001a,b).

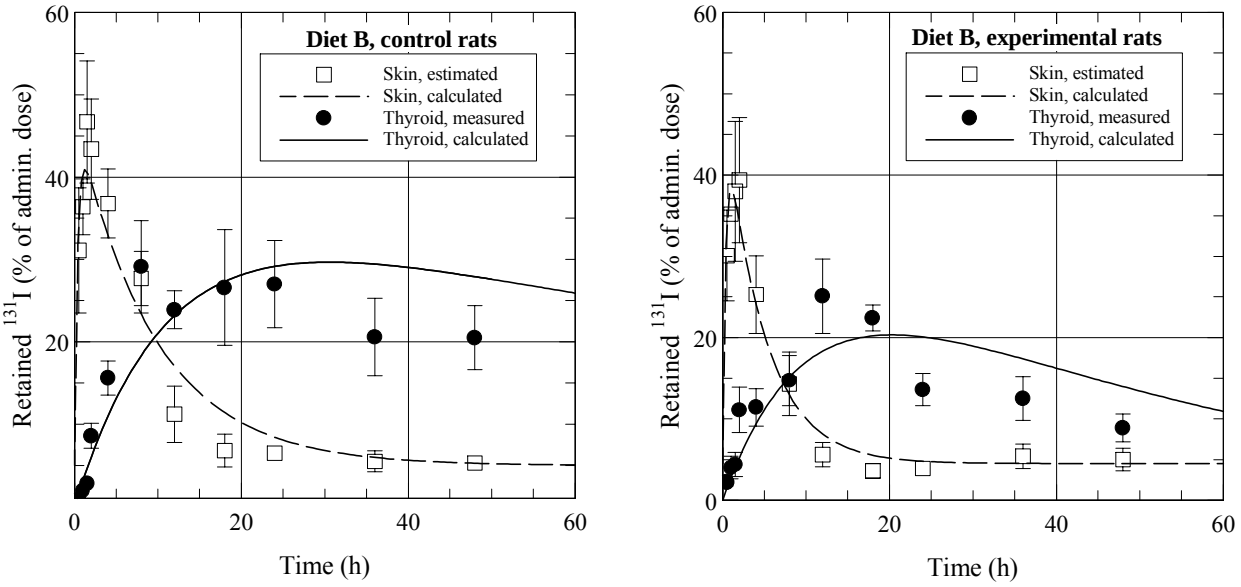

Fig. 2. Changes in ^{131}I radioactivity retained in the skin (□ estimated) and in the thyroid (● measured) of the control and experimental rats (n = 5-6 for each time point and each treatment) maintained on an iodine-sufficient diet (diet B), in dependence on the time after ^{131}I-iodide administration. Control rats drank distilled water and experimental rats drank distilled water with the addition of 5 g bromide per liter. [Adapted from Pavelka *et al.* (2001b)].

Interference of excessive bromide with the whole-body metabolism of iodine

In rats fed a semisynthetic purified diet containing a high concentration of bromide (up to 19.2 g NaBr/kg, ensuring an average daily intake of bromide of approximately 210-300 mg), Van Leeuwen *et al.* (1988) found a decrease in the body weight and marked changes in the morphology of the thyroid, a decrease in serum thyroxin accompanied by an increase in the concentration of TSH, and a decrease in the ^{125}I-iodide uptake by the thyroid. Similar signs of hypothyroidism were also described by Buchberger *et al.* (1990) in rats fed an iodine-poor diet with various amounts of added bromide (4-16 g NaBr/kg). Under these conditions, besides the above mentioned findings even death of experimental animals was encountered. In a series of experiments performed on adult male rats we also followed the effects

of a low, a moderate, and a high bromide intake, in addition to an extremely high bromide intake (> 200 mg Br^- per day), on the uptake of ^{131}I-iodide by various organs and tissues (including the thyroid) (Pavelka *et al.* 1999a, Vobecký *et al.* 1999). At the same time, the influence of an enhanced bromide intake on the kinetics of iodide uptake and elimination in the thyroid and skin (Pavelka *et al.* 2001b) and on the kinetics of iodine elimination from the body and on the value of the whole-body biological half-life of iodine were studied in these animals (Pavelka *et al.* 1999b, 2001a). Because the biological behavior of bromide depends on the state of iodine supply in the organism (Buchberger *et al.* 1990, Pavelka *et al.* 1999a), we performed our studies both under the conditions of sufficient iodine supply, and of a mild iodine deficiency.

In rats fed a diet with sufficient iodine supply (>25 μg I/day), the iodide accumulation in the skin predominated during the first hours after ^{131}I-iodide application. From this organ, radioiodide was gradually transferred into the thyroid. A high bromide intake (>150 mg Br^-/day) in these animals led to a marked decrease in iodide accumulation, especially by the thyroid, because of an increase in iodide elimination both from the thyroid, and from the skin (Fig. 2). In rats kept under the conditions of iodine deficiency (<1μg I/day), the iodide accumulation in the thyroid, but not in the skin, was markedly increased as a result of a thyrotropic stimulation. The effect of a high bromide intake (>100 mg Br^-/day) in these animals was particularly pronounced because the rates of iodide elimination were most accelerated both from their thyroid, and skin (Pavelka *et al.* 2001b).

A significant influence of a very high bromide intake (>160 mg Br^-/day) on the whole-body biological half-life of iodine was established. Very high bromide intake (i) decreased the amount of radioiodide accumulated in the thyroid, (ii) changed the proportion between the amount of iodine retained in the thyroid and the total amount of absorbed iodine, (iii) significantly shortened the biological half-life of iodine in the thyroid from approximately 101 h to 33 h in animals maintained on an iodine-sufficient diet and from 92 h to about 30 h in rats fed a low-iodine diet, and (iv) changed the time-course (added a further phase) of iodine elimination from the body. These changes were caused, with high probability, by an increase of iodine elimination by kidneys due to an excess of bromide. The overall picture of iodine elimination in animals fed the low-iodine diet was similar to that in animals maintained on iodine-sufficient diet (Pavelka *et al.* 2001a).

The effects of the highest dose of bromide administered to the rats (in drinking water with the addition of 5000 mg Br^- per liter, i.e. 5000 ppm) were observed, in addition to the thyroid, above all in the stomach and skin. At the same time, the effects of lower dose of bromide (500 ppm) were only marginal, and no effects of bromide were observed at the level of 50 ppm (Pavelka *et al.* 1999a, 2000c). The observed reduction of the food intake and consequently of the body weight gain and development in rats drinking water with the addition of the highest amount of bromide could be explained by the assumption that under the conditions of high bromide levels in the organism a disturbance in the physiological function of the stomach could arise. Because bromide is also concentrated in gastric mucosa and secreted into the stomach lumen (Gross 1962), possible changes in the composition of the digestive juice (e.g. production of hydrobromic acid) could disturb the digestive processes or could produce an organic disorder of the gastrointestinal system. The observed inhibition of the uptake of ^{131}I by the skin under the conditions of an enhanced bromide intake could also be fairly significant for the iodine metabolism in the rat because skin accounts for about 20 % of the rat body weight and represents the most important depot of both halogens. The observed effects of very high bromide intake on the thyroid gland and its function, notably in animals fed the low-iodine diet (e.g. markedly decreased 24-h uptake of ^{131}I-iodide, increased relative weight of the thyroid, decreased serum level of total thyroxine, etc.) were similar to those described previously.

We therefore suggest that high levels of bromide in the organism of experimental animals can influence their iodine metabolism in two parallel ways: by a decrease in iodide accumulation in the thyroid, and by a rise in iodide excretion by kidneys. A high surplus of bromide ions in blood, which is under our experimental conditions several thousand times greater than the concentration of iodide, can competitively inhibit the entrance of iodide into the thyroid, and replace a part of iodide in the gland by bromide. By accelerating the renal excretion of iodide, excessive bromide can also influence the pool of exchangeable iodide in the thyroid, in a similar way as chloride does (Pavelka *et al.* 1999b).

Impact of a high bromide intake in the lactating rat dam on iodine and bromide transfer to the suckling

Iodine is one of the essential substances indispensable for the survival, growth and development

of the young mammals. Since the intrathyroidal iodine stores of the neonate are low and the neonate's glandural machinery turns over nearly 100 % of its stores for its daily thyroid hormone production, the neonatal thyroid economy is extremely sensitive to fluctuations in the iodine supply from the mother (Glinoer 1997). An adequate supply of iodine to the neonate, for whom mother's milk is the sole source of this element, is ensured by the iodide-concentrating mechanism in the mammary gland of the mother. However, an enhanced bromide intake in the rat can markedly reduce the accumulation of iodide not only in the thyroid (Pavelka *et al.* 1999a, 2000c) and in the skin (Pavelka *et al*. 2001b) but also in the mammary gland (Lener *et al*. 2000). We decided, therefore, to examine the impact of high bromide levels in the organism of the mother on iodine transfer to the suckling and to study in greater detail the effects of a high bromide intake in lactating rats on the performance of the dams and on the prosperity of their young.

We found that the enhanced bromide intake in the dams significantly decreased the iodine transfer through mother's milk to the suckling. Moreover, the decrease in ^{131}I transfer was more pronounced in the young whose mothers drank water with the higher bromide concentration. High bromide intake in the lactating dams caused a decrease in iodide accumulation in the mammary glands, and an increase in iodide elimination through the kidneys of the dams. In the pups, we observed a significant decrease in the body weight gain and a significant increase in the relative weight of their thyroids with increasing bromide intake in their mothers. A prolonged intake of high amounts of bromide in the dams caused a marked hypothyroxinemia both in their own organism, and in the organisms of their pups. The effect of excess bromide was even more pronounced in the pups, as was evident from dramatically decreased concentrations not only of thyroxine but also of total triiodothyronine in sera of the young whose mothers drank water with the highest bromide concentration (Pavelka *et al*. 2002).

Very high intake of bromide in the dams in the course of the lactation period (about 220 mg Br^- per dam per day) caused a very significant decrease in the body weight increments in the suckling. Only about one-half of them survived and their general condition was very poor, although the amount of bromide in relation to the body weight received by these young was lower than that received by their mothers (Pavelka 2002). In the dams, there were two striking consequences undoubtedly caused by a high bromide intake: a stagnation in the extent of the consumption of diet and water in the course of the nursing period, and a conspicuous drop in the production rate of mother's milk (Pavelka 2003). We suggest that one of the possible reasons for the observed marked decrease in the production of mother's milk in the dams with high bromide intake could be a decreased stimulation of the mammary glands as a consequence of reduced consumption of mother's milk by their suckling. It is known that the intensity of lactation is regulated by the young. Provided that a high concentration of bromide in mother's milk constituted a serious obstacle for the young to receive the milk, the decline in the intensity of lactation and consequently also in the consumption of food and water by the dams would follow. Indeed, we have found that bromide ions ingested by the dams easily moved into the rat milk and were transferred *via* mother's milk in a large extent to the suckling. The amount of bromide in mother's milk depended on the bromide concentration in the drinking water taken by the dams. With the addition of 5 g bromide per liter (providing the mean daily bromide dose of 220 mg), bromide ions replaced about 54 % of the chloride in the milk (Vobecký *et al.* 2004). Although bromide passed easily through mother's milk into the body of the young, this transfer occurred at a much slower rate than the transfer of iodide (*cf.* Fig. 3 and Fig. 4). In the case of iodide, nearly 30 % of ^{131}I radioactivity applied to the mother appeared in the body of the young already in the course of the first 3 hours (Pavelka *et al.* 2002). In contrast, in the case of bromide, this amount was lower than 3 % after 3 hours from the application of ^{82}Br-bromide but it gradually increased during the next 22 hours (Pavelka 2003).

Our observation that bromide ingested by the dams readily moved into the milk and *via* mother's milk was transferred in a large extent to the suckling was not unexpected. Disse *et al.* (1996) found that bromide applied to pregnant female rats in the drinking water (2500 ppm NaBr) in the period between 5th and 15th days of gestation was transferred to embryos *via* placenta and later, up to 10 days after birth, although at decreasing concentrations, even to the offspring *via* milk. Significant delays in postnatal development were observed in all bromide-treated animals. Permanent deficits were recorded for body weight, brain weight and the protein content of brain tissue. Disse *et al.* (1996) suggested that pre- and perinatal exposure of rats to moderate concentrations of bromide might interfere with postnatal development including that of brain. However, as the authors stated, the exact mechanism of bromide action on developmental processes remains to be elucidated.

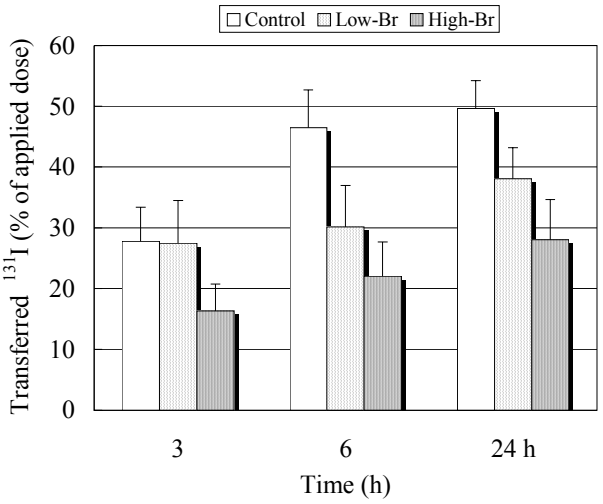

Fig. 3. Dynamics and extent of ^{131}I-iodine transfer from dams through mother's milk to the suckling (% of the dose applied to the dams), in dependence on bromide intake in the dams. Control dams drank distilled water and rats of the low-Br and high-Br groups drank distilled water with the addition of 1 g and 5 g bromide per liter, respectively. [Modified from Pavelka (2003)].

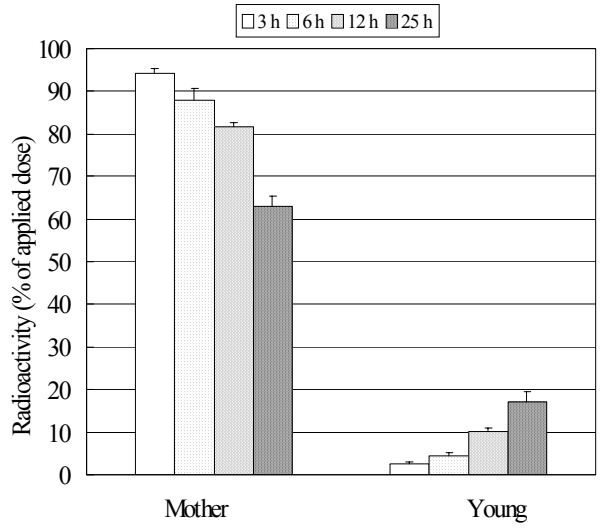

Fig. 4. Time-course of changes in the distribution of ^{82}Br radioactivity (applied to the dams) between the mother and the suckling, reflecting the transfer of bromide from dams through mother's milk to the young. [Modified from Pavelka (2003)].

Conclusions

Even though bromine is one of the most abundant and ubiquitous of the recognized trace elements in the biosphere, not enough information there is still available on the metabolism of bromide ion, the most common form of this element. This is concerned both the potential biological essentiality of bromide, and its toxic, especially goitrogenic effects. Nevertheless, some new findings about the biological behavior of bromide could be drawn from our recent experiments investigating the effects of high bromide intake in the rat, and especially in the lactating rat dam, on the metabolism of iodine in these animals:

i) Significant correlation between the steady-state concentration of bromide in 15 various organs and tissues of the rat and the corresponding values of the biological half-life of bromide was found in most tissues examined.

ii) The general assumption that the biological behavior of bromide in tissues is analogous to chloride is obviously not valid for the thyroid gland. We have proved that in this tissue, bromide did not replace chloride but rather iodide. Therefore, the thyrotoxicity of bromide is dependent upon the state of iodine supply in the organism.

iii) High levels of bromide in the organism of experimental animals can influence their iodine metabolism in two parallel ways: by a decrease in iodide accumulation in the thyroid and skin (and in the mammary glands in lactating dams), and by a rise in iodide excretion by kidneys. By accelerating the renal excretion of iodide, excessive bromide can also influence the pool of exchangeable iodide in the thyroid.

iv) A prolonged intake of high amounts of bromide in the dams caused a marked hypothyroxinemia both in their own organism, and in their pups. The effect of excess bromide was even more pronounced in the pups.

v) High bromide intake in the lactating rat dams dramatically decreased iodine and increased bromide transfer through mother's milk to the suckling. The impact of seriously decreased iodine content and increased bromide concentration in mother's milk on the young prosperity is detrimental.

Apart from the above partial achievements, however, it should be stated that the virtue of the toxic effects of bromide on the thyroid gland and mechnisms of its interference with the biosynthesis of thyroid hormones have not been so far elucidated.

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Reprint requests

Dr. Stanislav Pavelka, Department of Radiometry, Institute of Physiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 14220 Prague, Czech Republic, E-mail: pavelka@biomed.cas.cz, pav@chemi.muni.cz