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Biological Half-life of Bromide in the Rat Depends Primarily on the Magnitude of Sodium Intake

S. PAVELKA[1,2], A. BABICKÝ[3], M. VOBECKÝ[3]

[1]Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, [2]Department of Biochemistry, Faculty of Science, Masaryk University, Brno and [3]Institute of Analytical Chemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic

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Summary

The parallel course of the excretion rates of bromide and sodium ions was demonstrated in adult male and female rats administered simultaneously with potassium ^{82}Br-bromide and ^{24}Na-sodium chloride. The animals were exposed to various intakes of sodium ions accompanied with five different anions: Br^-, Cl^-, HCO_3^-, ClO_4^-, and SCN^-. Regardless of the anion accompanying the sodium ion, the excretion rates of $^{82}Br^-$ and $^{24}Na^+$ ions were proportional to the magnitude of sodium intake in the animals. Hence, we have proved our hypothesis that the biological half-life of bromide depends on the magnitude of sodium intake rather than on the intake of chloride.

Key words

Biological half-life • Bromide • Chloride • Sodium • Rat

Introduction

The mammalian body regulates both volume and ionic composition of the extracellular fluid (ECF), i.e. blood plasma and interstitial fluid. The major osmotically active solutes in the ECF are sodium and its attendant anions. Provided that the osmolality of intra- and extracellular fluids remains constant, changes in ECF volume will primarily reflect changes in the total body sodium content. The constancy of electrolyte concentration is achieved by active reabsorption of sodium in kidney tubules, whereas chloride (and bromide) mostly follows passively the movement of sodium. Thus, the control of urinary salt and water excretion is important for maintaining homeostasis of the body.

Elements from the same group of the periodic system have repeatedly been shown to exhibit certain similarities of metabolic behavior. This is particularly pronounced for the elements in group 7 (fluorine, chlorine, bromine, and iodine). The physiological significance of chloride ion has long been recognized. Rats fed a diet low in chloride had a retarded growth rate and symptomatology different from that observed with a sodium-deficient diet (Greenberg and Cuthbertson 1942). The therapeutic as well as the toxic effects of the element bromine are exerted by bromide, the ionic form of bromine. Although bromide-containing sedative drugs are now infrequently employed, intoxication with this halide and its attendant CNS symptoms remain a serious problem. The distribution (Pavelka *et al.* 2000) and action of bromide appears to be directly related to its

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

resemblance to other halides, chloride and, to a lesser extent, iodide (Pavelka 2004a,b). In the intestine, both chloride and bromide ions are completely passively absorbed by the paracellular pathway. The distribution of chloride and that of bromide are almost exclusively extracellular (Ullberg *et al.* 1964). Exceptions concern erythrocytes and acinar cells of the gastric wall. In the extracellular fluid, bromide ions replace an equivalent amount of chloride ions, the molar sum of total halides remaining constant at approximately 110 mmol/l. Both ions are predominantly excreted by the kidneys. The greater part of both halogen ions is reabsorbed in renal tubules after glomerular filtration and, due to the similarity in their physicochemical properties, bromide and chloride compete for tubular reabsorption (Rauws 1983).

The biological half-life of bromide can be shortened markedly by administering surplus of sodium chloride (Langley Czerwinski 1958). In fact, this is one of the major actions in the treatment of bromide intoxication (van Leeuwen and Sangster 1987). On the other hand, the already long half-life of bromide, which is about 12 days in humans (Söremark 1960) and approximately 3 to 8 days in the rat (Rauws and van Logten 1975, Pavelka *et al.* 2000), may be increased considerably by a salt-deficient diet. In the rat, bromide half-life was prolonged to 25 days on a salt-free diet (Rauws and van Logten 1975). This finding was interpreted by the authors as a marked dependence of the biological half-life of bromide on chloride concentration in the diet. However, keeping in mind the differences between the metabolism of sodium and chloride ions and the fact that sodium excretion rate depends on the magnitude of sodium intake, we have hypothesized (Babický *et al.* 2005) that the biological half-life of bromide depends on the magnitude of sodium intake rather than on the intake of chloride.

In order to test our hypothesis, in the present studies we simultaneously determined the biological half-life of bromide (using radionuclide ^{82}Br) and sodium (radionuclide ^{24}Na) which was accompanied with five different anions.

Methods

Animals and diets

Experiments were performed on adult Wistar rats: 15 females and 10 males of an average body weight of 268±17 g and 441±27 g, respectively. All the animals were fed a special, low-sodium pelleted diet (Bergman, Kocanda, Czech Republic) with a mean concentration of sodium of 284±20 mg/kg (12.3 mEq/kg) and normal levels of potassium and magnesium of about 6730 and 1750 mg/kg, respectively. Dietary concentration of bromine was 3.5±0.2 mg/kg (0.04 mEq/kg) and that of chlorine was 588±33 mg/kg (16.6 mEq/kg). Concentrations of Na, K, Mg, Br, and Cl in the diet were determined by instrumental neutron activation analysis in a mode of short-term activation (Vobecký *et al.* 2000), and in the case of Na and K also by a long-term activation. The experimental design is shown in Table 1. The rats were arranged into five groups, each consisting of three females and two males. Animals in the first group drank distilled water with the addition of NaBr, in the second group with NaCl, in the third group with $NaHCO_3$, in the fourth group with $NaClO_4$, and animals in the fifth group drank water with the addition of NaSCN. Concentrations of the solutions of these salts were 50 and 100 mmol/l in the case of females and males, respectively. During the whole experimental period, diet and drinking fluids were provided *ad libitum.* The rats were housed individually in plastic cages under standard conditions. The body weight of each rat as well as their consumption of diet and drinking fluid were recorded at regular intervals.

Table 1. Experimental arrangement of different sodium salts administered in drinking fluid.

Group	Sex	Number of animals	Salt	Concentration (mmol/l)
1	F	3	NaBr	50
	M	2	"	100
2	F	3	NaCl	50
	M	2	"	100
3	F	3	$NaHCO_3$	50
	M	2	"	100
4	F	3	$NaClO_4$	50
	M	2	"	100
5	F	3	NaSCN	50
	M	2	"	100

Simultaneous determination of biological half-lives of bromide and sodium

After establishing constant drinking regimens,

on the 14th experimental day all the animals were given simultaneously approximately 1.7 MBq ^{82}Br (about 0.25 mg Br) in the form of potassium bromide and 1.8 MBq ^{24}Na (about 0.35 mg Na) in the form of sodium chloride in 0.3 ml saline by subcutaneous injection. Obviously, these amounts of Br^- and Na^+ ions injected with the radioactive preparations were negligible. The retained ^{82}Br and ^{24}Na radioactivity was measured *in vivo* (at the time intervals of 15, 39, 63, 87, 111, 135, 159, and 183 h after the application of radionuclides) by means of a computerized gamma-spectrometric system equipped with an HPGe detector (Canberra). Details of the whole-body measurement of radioactivity are given in our previous paper (Vobecký *et al.* 2005).

The time course of the changes in the whole-body ^{82}Br (^{24}Na) radioactivity of the experimental animal can be expressed by the equation:

$$R_t = A\,[\exp(-0.693\ t/T_{el})] \qquad (1)$$

where R_t is the ^{82}Br (^{24}Na) radioactivity retained in the rat at time t expressed as the % of the applied dose A, T_{el} is the half-life of the ^{82}Br (^{24}Na) elimination from the animal's body (given in hours), and t is the time which elapsed from the moment of the ^{82}Br (^{24}Na) application to the animal (given in hours).

The radionuclides ^{82}Br (half-life of radioactive decay equal to 35.3 h) and ^{24}Na (physical half-life equal to 15 h) were prepared by irradiating the KBr and NaCl targets with neutrons in the core of the LWR-15 research nuclear reactor (Nuclear Research Institute, Řež near Prague) for 1 h at 9 MW power outputs.

Statistics

The correlation between the biological half-life of bromide and the magnitude of sodium intake was evaluated by Pearson´s correlation coefficient, applied to values determined in individual animals exposed to various intakes of sodium ions accompanied with four different anions. Likewise, the correlation between bromide and sodium half-lives was evaluated by Pearson´s correlation coefficient, but applied to group mean values.

Table 2. Mean daily intakes of diet and drinking solutions throughout the experimental period, mean body weight of rats on the 14th and the 22nd day of the experiment, and average values of the 8-day body weight gain in individual groups of animals

Group	Sex	Mean daily intake		Body weight (g)		
		Diet (g)	Solution (ml)	14th day	22nd day	8-day gain
1	F	21.3 ± 1.6	36.8 ± 14.7	258 ± 17	254 ± 18	−4
	M	14.8 ± 6.8	22.4 ± 2.3	457 ± 15	424 ± 40	−33
2	F	17.4 ± 3.4	32.0 ± 6.8	280 ± 10	284 ± 14	4
	M	30.7 ± 0.7	59.7 ± 6.2	459 ± 44	478 ± 38	19
3	F	17.4 ± 2.0	31.7 ± 2.8	265 ± 17	270 ± 18	5
	M	28.1 ± 1.9	60.7 ± 5.6	434 ± 29	468 ± 53	34
4	F	15.3 ± 0.8	31.5 ± 3.6	260 ± 21	261 ± 20	1
	M	25.6 ±0.8	51.0 ± 22.6	446 ± 17	458 ± 22	12
5	F	18.0 ± 2.7	28.4 ± 5.8	285 ± 7	290 ± 11	5
	M	21.2 ± 1.1	25.3 ± 3.9	425 ± 4	421 ± 6	−4

Values are means ± S.D.

Results

Daily intake of the diet and salt solutions throughout the experimental period as well as mean body weight of rats on the 14th and the 22nd day of the experiment (at the end of the experimental period) in particular groups of animals are summarized in Table 2. It is evident that an increased intake of various sodium salts did not noticeably influence the growth of the animals. Table 3 gives the estimated values of mean daily intake of sodium and the corresponding average values of simultaneously determined biological half-lives of bromide and sodium ions and the Br/Na half-life ratios in individual groups.

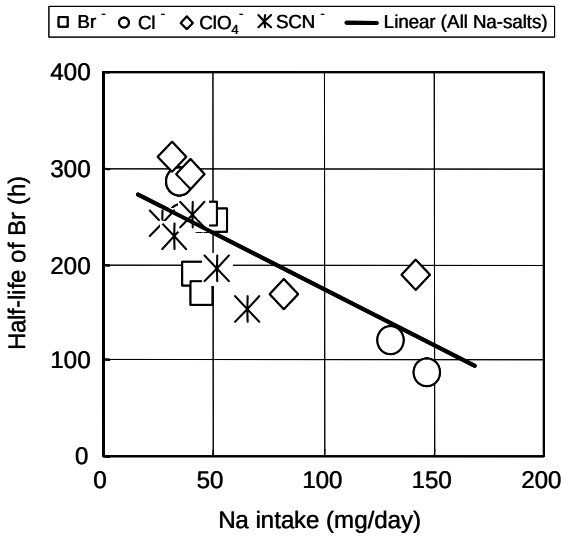

Fig. 1. Dependence of the biological half-life of bromide on mean daily intake of sodium. The straight line is fitted by linear regression analysis of the values determined in individual animals receiving sodium accompanied with the specified anions.

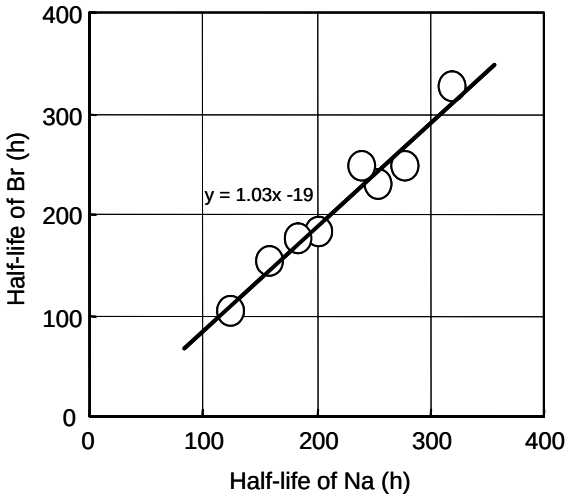

Fig. 2. Correlation between the rate of excretion of bromide and sodium ions. Each symbol represents the mean of bromide and sodium half-life values, measured in 2-3 animals receiving sodium in the form of solutions of sodium bromide, chloride, perchlorate and thiocyanate in the amounts specified in Table 3.

Table 3. Mean daily intake of sodium throughout the experimental period, mean values of the half-life of ^{82}Br-bromide and ^{24}Na-sodium excretion, and average values of the Br/Na half-life ratios in individual groups of animals receiving sodium accompanied with different anions (Br^-, Cl^-, HCO_3^-, ClO_4^-, and SCN^-)

Group	Sex	Na intake (mg/day)	Half-life		
			Br (h)	Na (h)	Br/Na
1	F	49.4 ± 5.4	229 ± 35	256 ± 44	0.89
	M	52.6 ± 6.5	153 ± 24	159 ± 40	0.96
2	F	41.3 ± 5.3	248 ± 0	240 ± 8	1.03
	M	142.3 ± 11.7	104 ± 23	124 ± 29	0.84
3	F	39.8 ± 2.2	319 ± 31	295 ± 128	1.08
	M	142.0 ± 12.4	(330 ± 12)†	(99 ± 4)†	-
4	F	37.8 ± 4.2	325 ± 18	321 ± 147	1.01
	M	114.7 ± 42.8	181 ± 15	202 ± 33	0.89
5	F	35.8 ± 6.9	248 ± 7	278 ± 132	0.89
	M	61.4 ± 9.8	175 ± 30	185 ± 78	0.95

Values are means ± SD. †Not included in the subsequent data evaluation.

Figure 1 shows that the measured values of the biological half-life of bromide are inversely proportional to the magnitude of sodium intake in the animals, regardless of the type of anion accompanying sodium ions. The correlation between the half-life of bromide and the intake of sodium was found to be significant ($r = –0.76$, $p<0.05$). At the same time, the average values of the biological half-life of bromide closely follow those of sodium half-life, again irrespectively of the type of sodium salt solutions administered to the rats in the individual experimental groups (Fig. 2), with the exception of sodium bicarbonate (see later). The correlation between the determined values of bromide and sodium half-lives was highly significant ($r = 0.96$, $p<0.001$).

Discussion

The data obtained in the present experiments (Table 3, Figs 1 and 2) clearly show that the rates of excretion of bromide and sodium ions run in parallel in the rats maintained under the same conditions as regards

the magnitude of sodium intake and metabolic activity. The only exception was the biological half-life of bromide in male rats in the third experimental group. These animals were characterized by enormously long biological half-life of bromide, markedly different from the short half-life of sodium in this group. Most probably, an immediate cause of this discrepancy was the large amount of administered bicarbonate ions that altered the blood acid-base equilibrium and produced alkalosis in the animals. The kidneys of these animals obviously excreted the surplus bicarbonate ions at the expense of bromide and chloride ions. Therefore, the discrepant values obtained in these animals maintained under non-physiological conditions were omitted in Figures 1 and 2.

In our previous paper (Babický *et al.* 2005), we have already demonstrated the parallel course of the excretion rates of sodium and bromide ions in rats which had simultaneously received the radionuclides ^{24}Na and ^{82}Br. However, in that paper the experimental animals were maintained on various sodium intakes but sodium ions were applied solely in the form of differently concentrated sodium chloride solutions. Obviously, the present arrangement of feeding sodium ions accompanied with other than chloride anions (Table 1) reasonably extended the validity of our previous conclusions and refuted any objections against possible interference of chloride anions with the effect of sodium ions.

Because bromide is excreted slowly and practically completely in the urine, total body chloride may be followed for a considerable time after a single dose of bromide (Hellerstein *et al.* 1960). As the rat tissues show consistent agreement between the ratios of chloride to bromide in the serum, liver, skin and muscle (Hellerstein *et al.* 1960), we assume that it is justifiable to use radioactive ^{82}Br-bromide for following the excretion rate of chloride as well. In addition, due to the close relation of sodium ions and the attendant anions, the excretion rate of sodium could also be followed by using ^{82}Br-bromide. The achieved results of the simultaneous determination of biological half-lives of sodium and bromide in the rats maintained on various sodium intakes in the present experiments (Figs 1 and 2) and also in our previous experiments (Babický *et al.* 2005) corroborate this assumption.

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Reprint requests

S. Pavelka, Institute of Physiology, Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20 Prague 4, Czech Republic. E-mail: pavelka@biomed.cas.cz