Sodium-Iodide Symporter Mediates Iodide Secretion in Rat Gastric Mucosa *In Vitro*

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***In vivo* studies on rats have demonstrated that considerable amounts of iodide are transported from the bloodstream into the gastric lumen. The mechanisms for and functional significance of this transport are poorly understood. Active (driven by Na^+/K^+-ATPase) iodide transport into thyroid follicular cells is mediated by the sodium-iodide symporter (NIS), which is also abundantly expressed in gastric mucosa. We aimed to further investigate the iodide transport in gastric mucosa and the possible role of NIS in this transport process. Iodide transport in rat gastric mucosa was studied *in vitro* in an Ussing chamber system using ^{125}I as a marker. The system allows measurements in both directions over a mucosal specimen. A considerable transport of iodide (from the serosal to the mucosal side) was established across the gastric mucosa, whereas in the opposite direction (mucosa to serosa), iodide transport was negligible. Sodium perchlorate ($NaClO_4$), a competitive inhibitor of NIS, and ouabain, an inhibitor of the Na^+/K^+-ATPase, both attenuated gastric iodide transport from the serosal to the mucosal side. To investigate a possible neuroendocrine regulation of the iodide transport identified to occur from the serosal to the mucosal side of the stomach, thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), histamine, or nitric oxide donor S-nitroso-N-acetyl-D,L-penicillamine (SNAP) was added. None of these substances influenced the iodide transport. We conclude that iodide is actively transported into the gastric lumen and that this transport is at least partly mediated by NIS. Additional investigations are needed to understand the regulation and significance of this transport.** Exp Biol Med 231:277–281, 2006

Key words: gastric NIS; gastric iodide secretion; ouabain; sodium perchlorate; Ussing chamber

Introduction

Iodide is transported from the bloodstream into the gastric lumen in considerable amounts *in vivo* (1–3). The mechanisms for and functional significance of this transport are as yet poorly understood.

Active iodide transport into thyroid follicular cells is mediated by the sodium-iodide symporter (NIS) (4), which is also abundantly expressed in gastric mucosa (3, 5–7). Thyroidal NIS has been extensively investigated (8) since the cDNA sequence of rat NIS was revealed (9). NIS is a transmembrane glycoprotein actively pumping iodide into the thyroid follicular cells against a gradient, and it is driven by the Na^+-gradient generated by Na^+/K^+-ATPase (4).

Gastric NIS is preferentially localized basolaterally in the surface epithelial cells (3), but little is known about function and regulation of NIS in gastric mucosa. It is noteworthy that during the 1960s perchlorate- and thiocyanate-sensitive iodide transport was suggested to occur across the gastric mucosa in rats, dogs, and humans (1). The occurrence of iodide transport from the circulation to the gastric lumen was recently confirmed in an *in vivo* model in rats (3). In this report gastric iodide transport is suggested to be mediated by NIS as part of an entero-thyroid recirculation of iodide. This is in line with the observation, described decades ago, that iodide transport into the gastric lumen serves as an important iodide-conserving mechanism in bovines (2). Other possible functions suggested for gastric secretion of iodide are antioxidative (10) and antimicrobial (6).

The causal relationship between the occurrence of both NIS protein and NIS mRNA in gastric mucosa and the accumulation of iodide in the stomach after administration of radioactive iodide has not been established. Gastric NIS

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was suggested to mediate uptake of iodide across gastric mucosa (5). However, *in vivo* experiments failed to identify any gastric iodide uptake but showed a marked secretion of iodide into the gastric lumen (3). Therefore, we sought to further investigate the extent and mechanisms of iodide transport in gastric mucosa in an *in vitro* model. The competitive NIS inhibitor perchlorate and the Na^+/K^+-ATPase inhibitor ouabain were used to establish whether gastric NIS contributes in the transport process. The possible regulation of gastric iodide transport by biologically active substances was also tested by the addition of thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), histamine, or nitric oxide (NO)-donor S-nitroso-N-acetyl-D, L-penicillamine (SNAP).

Materials and Methods

Animals. A total of 73 male Sprague-Dawley rats (200–250 g) (Taconic M&B, Denmark, or Scanbur BK, Sweden) were used. The animals had free access to standard food pellets and tap water. The animals were killed by bleeding from a cardiac incision during deep isofluran anesthesia and the stomachs were removed. Animal care was in accordance with the European Council Convention of 1986, as well as the National Institutes of Health, USPHS, Guide for the Care and Use of Laboratory Animals. The study was approved by the research animal ethics committee of Malmö and Lund, Sweden.

Specimens. The oxyntic part of the stomach was removed, emptied of contents, and divided along the major and minor curvatures to yield two separate specimens. The specimens were pinned to a Sylgaard-coated Petri dish filled with oxygenated Krebs' buffer solution at room temperature, and the muscular layer was stripped off using fine forceps and scissors before mounting the mucosal layer in the Ussing chamber. Pars proventricularis, known to lack NIS expression (3), from four rats were used as reference specimens.

***In Vitro* Studies of Iodide Transport.** Ussing chambers (Navicyte; San Diego, CA) with round apertures of 0.64 cm^2 were used. After tissue mounting, the chambers were immediately placed in a heat block maintaining 37°C. The two reservoirs were each filled with 1.5 ml of modified Krebs' buffer solution (NaCl 110.0 m*M*, $CaCl_2$ 3.0 m*M*, KCl 5.5 m*M*, KH_2PO_4 1.4 m*M*, $NaHCO_3$ 29.0 m*M*, Na pyruvate 5.7 m*M*, Na fumarate 7.0 m*M*, Na glutamate 5.7 m*M*, and glucose 13.4 m*M*; pH 7.4) and continuously aerated with a mixture of 95% O_2 and 5% CO_2. After 15 mins of equilibration, the solution in one reservoir was replaced with fresh 37°C Krebs' buffer and in the other with Krebs' buffer containing 0–200 m*M* NaI supplemented with 0.1 ml of a 0.08 μ*M* ^{125}I solution, yielding a radioactivity of 0.2 MBq, in order to identify iodide transport across the mucosa. Iodide was added either to the serosal or to the mucosal side reservoir. To calculate iodide transport, samples of 150 μl were drawn from the iodide-containing (donor) reservoir at 0 and 60 mins (end of the experimental period) and from the other (receiver) reservoir at 15, 30, 45, and 60 mins. Samples taken at 15, 30, and 45 mins were replaced by an equal volume of fresh Krebs' buffer. In a first set of experiments, different doses of iodide and the direction of iodide transport were studied. Specimens were mounted with the donor reservoir either on the serosal side or on the mucosal side. Because these experiments revealed that the direction of iodide transport was from the serosal to the mucosal reservoir, separate series of experiments were designed accordingly in order to test possible inhibitory effects of perchlorate (20 m*M*) and ouabain (500 μ*M*) on iodide transport. In this experimental set up, all specimens were mounted with the donor reservoir (0.2 m*M* NaI and 0.2 MBq ^{125}I) on the serosal side, and the inhibitor under investigation was added to both reservoirs throughout the experiment, including the equilibrating period. In order to maintain constant concentration, inhibitor was also added to the buffer used for replacement after sampling. In a separate series of experiments (0.02 m*M* NaI and 0.2 MBq ^{125}I in the donor reservoir), the possible regulation of the iodide transport was investigated by the addition of TSH (0.1 U/ml), TRH (1 or 10 μ*M*), VIP (0.1 or 1 μ*M*), histamine (0.1 m*M*), or NO donor SNAP (0.1 m*M*) to both sides of the specimen. These experiments were carried out as described earlier.

All samples were measured for radioactivity using a Packard Cobra II auto-gamma counting system. Transport was expressed as nmol iodide cumulated at each time point with correction for the removed sample volumes.

As an indicator of mucosal viability, the transepithelial potential differences were measured before and at the end of each experiment using a pair of Ag/AgCl electrodes embedded in KCl agar. Potential differences were 1–7 mV before experiments and 1–12 mV after experiments. Specimens with extremely low (<1 mV) or greatly diminishing potential differences, as well as some exhibiting obvious leakage of iodide, were excluded ($n = 20$).

Chemicals. Isofluran (Forene) was obtained from Apoteket AB (Stockholm, Sweden). ^{125}I was obtained from Amersham Biosciences (Amersham, UK) and diluted to 2 MBq/ml in saline. Sodium iodide (NaI), sodium perchlorate ($NaClO_4$), ouabain, TSH, TRH, VIP, histamine, and SNAP were purchased from Sigma-Aldrich (Stockholm, Sweden). Ouabain was solubilized in boiling water to 3 m*M*, and SNAP was solubilized in dimethyl sulfoxide (DMSO) to 10 m*M* before further dilution in buffer solution. All other chemicals were solubilized in distilled water or saline before further dilution in buffer solution.

Statistics. Values are presented as medians (interquartile range). Comparisons between groups were done with Mann-Whitney *U* test except when several doses were compared (VIP and TRH), in which case Kruskall-Wallis test was used. *P* values of < 0.05 were considered significant. Statistical analysis was performed using StatView 4.01 software (Abacus Concepts, Berkeley, CA). Results in the

figures are presented as boxplots showing median, quartiles, and whiskers drawn to the extreme values, except in Figure 1 where the total ranges are shown.

Results

Amount and Direction of Iodide Transport. The ability to transport iodide across gastric mucosa was tested by the addition of a wide range of different iodide concentrations (5.3 n*M*–200 m*M*) to either the serosal or the mucosal side reservoir. These experiments revealed that an increase in iodide concentration on the serosal side resulted in increased transport to the mucosal side (Fig. 1). Iodide 0.02 m*M* added to the serosal side reservoir yielded a transport to the mucosal side of 0.96 (0.86–1.1) nmol after 60 mins ($n = 11$). With an initial iodide concentration of 0.2 m*M* in the serosal side reservoir, iodide transport to the mucosal side was 9.0 (7.3–9.1) nmol after 60 min ($n = 11$). Negligible amounts of iodide were transported in the opposite direction; that is, addition of 0.02 m*M* iodide to the mucosal side reservoir resulted in the transport of 0.23 (0.16–0.26) nmol at 60 min ($n = 8$) (Fig. 2). The iodide transport across gastric mucosa was linear over time and directed from the serosal to the mucosal side (Fig. 2).

Pars proventricularis of rat stomach was used as a reference specimen, and in this specimen no transport was detected in either direction (data not shown).

Inhibition of Iodide Transport by Perchlorate. The presence of perchlorate in the Ussing chamber inhibited gastric mucosal transport of iodide (0.2 m*M* = 300 nmol/specimen) from the serosal to the mucosal side by 47% ($P = 0.0027$). Iodide transport was 5.1 (4.8–6.3) nmol to the mucosal side after 60 min with 20 m*M* perchlorate on both sides of the specimen ($n = 7$). The transport in specimens ($n = 6$) run in parallel from the same animals, but without the addition of perchlorate, was 9.6 (9.2–9.8) nmol (Fig. 3A).

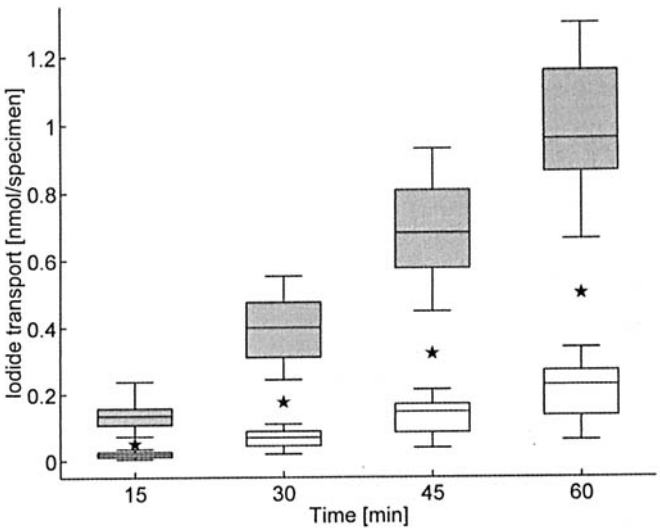

Figure 2. Boxplots showing iodide transport from serosal to mucosal side (shadowed boxes, $n = 11$) and from mucosal to serosal side (open boxes, $n = 8$). Values are nmol transported per specimen (0.64 cm^2) after 15, 30, 45, and 60 mins; medians (interquartile range); whiskers drawn to the extreme values. Initial iodide concentration was 0.02 m*M*. *$P < 0.001$ at all time points.

Inhibition of Iodide Transport by Ouabain. Presence of ouabain in the Ussing chamber inhibited gastric transport of iodide (0.2 m*M* = 300 nmol/specimen) from the serosal to the mucosal side by 23% ($P = 0.009$). Iodide transport was 7.3 (4.8–7.9) nmol to the mucosal side after 60 mins with 500 μ*M* ouabain on both sides of the specimen ($n = 5$). The transport in specimens ($n = 5$) run in parallel from the same animals (but without the addition of ouabain) was 9.5 (9.1–9.9) nmol (Fig. 3B).

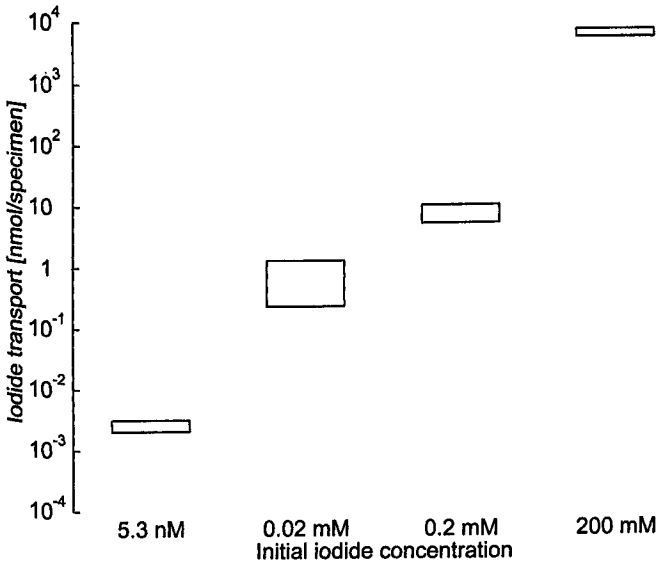

Figure 1. Boxes showing total range of transport for each tested iodide concentration. Values are nmol transported per specimen (0.64 cm^2) after 60 min. For initial iodide concentration, 5.3 n*M*, $n = 4$; 0.02 m*M*, $n = 17$; 0.2 m*M*, $n = 11$; and 200 m*M*, $n = 2$.

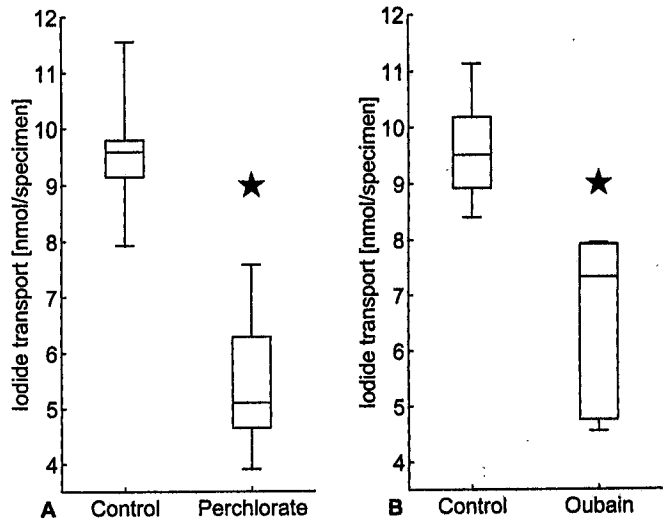

Figure 3. Boxplots showing iodide transport from the serosal to the mucosal reservoir in the presence of perchlorate 20 m*M* (A) or ouabain 500 μ*M* (B). Initial iodide concentration was 0.2 m*M*. Values are nmol transported per specimen (0.64 cm^2) after 60 min; medians (interquartile range); whiskers drawn to the extreme values, $n = 5$–7. *$P < 0.01$ in A and B.

Table 1. Iodide Transport (nmol/Specimen in 60 Min) With and Without TSH, TRH, VIP, Histamine, and NO Donor SNAP[a]. Initial Iodide Concentration Was 0.02 m*M*.

Test substance	Transport	*n*	Transport controls	*n* controls
TSH 0.1 U/ml	0.53 (0.66–1.0)	7	0.49 (0.71–0.82)	5
TRH 1 μ*M*[b]	0.94 (0.63–1.4)	4	1.2 (1.0–1.3)	4
TRH 10 μ*M*[b]	1.3 (1.2–1.5)	4	1.2 (1.0–1.3)	4
VIP 0.1 μ*M*[c]	1.2 (1.1–1.2)	5	0.97 (0.89–1.0)	6
VIP 1 μ*M*[c]	1.1 (1.0–1.3)	7	0.97 (0.89–1.0)	6
Histamine 0.1 m*M*	0.77 (0.62–0.96)	4	0.78 (0.60–0.98)	4
SNAP 0.1 m*M*	0.75 (0.59–0.84)	6	0.66 (0.55–0.82)	7

[a] Values are median (interquartile range).
[b] Controls are the same for both doses of TRH.
[c] Controls are the same for both doses of VIP.

Effects of TSH, TRH, VIP, Histamine, and SNAP on Gastric Iodide Transport. Iodide transport from the serosal to the mucosal side was measured in the presence of TSH (0.1 U/ml, $n=7$), TRH (1 μ*M*, $n=4$ or 10 μ*M*, $n=4$), VIP (0.1 μ*M*, $n=5$ or 1 μ*M*, $n=7$), histamine (0.1 m*M*, $n=4$), or SNAP (0.1 m*M*, $n=6$) (Table 1). None of these substances caused any statistically significant changes in the rate of iodide transport. For each substance, specimens that were run in parallel but without the addition of test substance served as controls ($n = 4$–7). Initial iodide concentration in this series was 0.02 m*M*.

Discussion

Iodide transport into the thyroid follicular cell is mediated by NIS, which is a transmembrane protein actively transporting iodide together with sodium (4). Iodide transport in the stomach may also be mediated by NIS since NIS is abundantly expressed in gastric mucosa (3, 7). NIS is predominantly localized basolaterally in the surface epithelium of the gastric mucosa, and thus it is reasonable to assume that NIS mediates transport of iodide into the epithelial cells as it does in thyroid follicular cells. The subsequent efflux of iodide into the gastric lumen may be passive or mediated by some other as yet unknown system. Pendrin, which mediates iodide transport from the thyroid follicular cell into the colloid (11), is one putative candidate. However, no pendrin has been found within the gastric mucosa (12).

The Ussing chamber is a well-established *in vitro* model for studies on transport of and permeability for various types of substances through epithelia (13, 14). In the present study, the Ussing chamber model was adapted for studying iodide transport across rat gastric mucosa. Iodide transport was found to be considerable from the serosal to the mucosal side but negligible in the opposite direction, suggesting that the route of iodide transport is from the circulation into the gastric lumen and that no uptake of iodide takes place in the gastric mucosa. This is in accordance with previous *in vivo* findings of Josefsson *et al.* (3). In this study radioactive iodide administered *via* an intragastric tube to rats subjected to ligation of pylorus could not be retrieved in the circulation or in the thyroid, indicating lack of uptake via the gastric mucosa. In addition, it was shown that ^{125}I given intravenously accumulated in both the stomach lavage and the gastric wall.

There are several established competitive inhibitors of the NIS-mediated iodide transport in the thyroid, including such anions as bromide (Br^-), chlorate (ClO_3^-), perchlorate (ClO_4^-), and thiocyanate (SCN^-). In the present study, perchlorate (the most widely used and well-characterized inhibitor of NIS activity and acting highly competitively in iodide transport) was used (15, 16). Perchlorate inhibited the iodide transport from serosal to mucosal side by 47%, which indicates that NIS is a putative candidate for mediating this transport. It is noteworthy, however, that in spite of using a high concentration of perchlorate, a total inhibition of iodide transport, as reported to occur in cultured NIS expressing cells (16, 17), could not be achieved. This probably reflects that the availability of the NIS molecule to perchlorate is different in cultured cells and full-thickness mucosa *in vitro*. In order to facilitate diffusion, the muscular layer of the stomach wall was removed before mounting the mucosa in the Ussing chamber. However, a substantial amount of connective tissue still remains in the lamina propria and in the submucosa, which hampers the possibility for both iodide and perchlorate to reach NIS located in the apical mucosa. Perchlorate, which is a larger molecule than iodide, is probably most affected by such impediments. In an attempt to overcome this we therefore added perchlorate, as well as ouabain, to both the donor and the receiver chambers.

Iodide transport mediated by NIS is dependent on Na^+/K^+-ATPase (16). To further test the hypothesis that NIS mediates gastric iodide transport, we used ouabain, which is an inhibitor of Na^+/K^+-ATPase. Presence of ouabain attenuated the iodide transport from the serosal to the mucosal side by 23%. Besides low availability caused by diffusion impediments, the lack of total inhibition by both perchlorate and ouabain may indicate that NIS-mediated transport is not the only route by which iodide can pass the gastric mucosa. From the present results we conclude that NIS mediates at least part of the substantial iodide transport from the bloodstream over the gastric mucosa and into the gastric lumen.

In order to identify a possible neuroendocrine regulation of gastric NIS activity, we also tested whether TSH, TRH, VIP, histamine, or NO influenced gastric iodide transport. TSH is known to regulate thyroid iodide uptake activity mainly by increasing NIS expression and synthesis, but regulation of NIS activity has also been suggested (18). It was therefore of interest to test the effects of TSH in our system, measuring gastric iodide transport *in vitro*. TRH, VIP, histamine, and NO are all important messengers in the gastric mucosa, mediating or modulating a number of physiological activities, such as vasodilatation and acid and bicarbonate secretion (for a review, see Ref. 19). In the present study, none of these putative regulatory substances was found to affect gastric iodide transport. It must, however, be emphasized that the present experimental conditions only allow studies on acute regulatory effects and that changes in, for example, NIS mRNA synthesis, are beyond detection. The lack of response to the tested neuroendocrine signaling substances may, as previously suggested for perchlorate and ouabain, also be due to diffusion impediments.

In order to understand the regulation of NIS expression and activity in the gastric mucosa as well as the functional significance of iodide transport into the gastric lumen, additional work is needed. A challenging aspect of iodide function worth exploring is its suggested antimicrobial effect. A recent study reported that the presence of iodide increases the antimicrobial activity of acidified nitrite, thereby augmenting the activity of gastric acid, thus providing a better host defense against bacteria (20). In this context we must also consider that the anion selectivity of NIS is $ClO_4^- > ReO_4^- > SCN^- > I^- > NO_3^- > Br^- > Cl^-$ (15, 21). This leaves us with the possibility that the main role of gastric NIS may be transportation of anions other than iodide. An interesting putative candidate is nitrate because nitrate is a source for nonenzymatic NO production, which abundantly occurs in the stomach (22, 23). Salivary accumulation and secretion of dietary nitrate followed by reduction to nitrite by bacterial nitrate reductases and formation of NO at low pH are considered to be the mechanisms. Secretion *via* gastric NIS offers an additional possibility to increase local nitrate concentration in the gastric juice. Noteworthy is that NIS is found also in salivary glands (3), and its role in mediating nitrate accumulation and transport in this location is as yet unexplored.

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