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Sodium Iodide Symporter (NIS) in Gastric Mucosa: Gastric Iodide Secretion

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Abstract

Iodide is actively transported from the bloodstream into the gastric juice and some iodide accumulation occurs in the gastric wall, but no uptake of iodide takes place in the gastric lumen. The cDNA-sequence of the thyroid sodium–iodide symporter (NIS) was revealed in 1996 and, in the thyroid gland, iodide is actively transported into the thyrocyte by NIS. Later on NIS was also found to be present, in large amounts, in the gastric mucosa, where it is located basolaterally in the surface epithelial cells. Iodide transport over the gastric mucosa is attenuated by the selective competitive NIS inhibitor perchlorate, and also by ouabain, an inhibitor of Na^+/K^+-ATPase, which powers NIS transport. Thus, gastric iodide secretion is to a large extent mediated by NIS. The regulation of gastric NIS expression is still unknown. The functional role of NIS in the gastric mucosa is uncertain, but several theories have been put forward. These include mediating recirculation of iodide, as well as securing the presence of iodide in the stomach for antimicrobial or antioxidative purposes. Gastric iodide secretion may also be a protecting mechanism against developing gastric cancer. Gastric NIS has further been suggested to be an important protein for transporting anions other than iodide, i.e., nitrate. In the future NIS expression, or lack thereof, may become a useful parameter in the diagnosis of gastric cancer. Gene transfer of NIS into cancer cells without NIS expression, as well as chemical induction of NIS expression, are methods under exploration. If means to regulate NIS expression in tumor cells are found, it may become possible to use radioiodine therapy in gastric cancer.

another possibility: enables excretion, as with sweat and CSF (located in the choroid)

twisted but typical!

Abbreviations

BSA	Bovine serum albumin
cDNA	Complementary deoxyribonucleic acid
E17	Embryonic day 17
FITC	Fluorescein isothiocyanate
^{131}I ^{125}I	Radioactive isotopes of iodine
mRNA	Messenger ribonucleic acid
Na^+/K^+-ATPase	Sodium–potassium adenosine triphosphatase
NIS	Sodium iodide symporter
RT-PCR	Reverse transcriptase-polymerase chain reaction
^{35}S-dATP	Radioactive sulfur isotope linked to deoxyadenosine triphosphate
SNAP	S-nitroso-*N*-acetyl-D, L-penicillamine
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
VIP	Vasoactive intestinal peptide

Introduction

The absorption, distribution and elimination of iodide as an essential, but in some geographical areas rare, nutrient have interested researchers for many years. When radioactive isotopes of iodide became readily available in the middle of the last century, the physiological role of iodide, as well as its therapeutic potential, became the focus of interest for several decades, as described in a review by Brown-Grant (1961). During this period of intensive research, it was established that iodide is absorbed from the small intestine, actively taken up by the thyroid, and incorporated as an essential constituent of thyroid hormone. Iodide is further found to be stored within the thyroid to meet future needs. Interestingly, a substantial iodide concentration, independent of acid secretion, was also found in the gastric juice. An intriguing discovery was that some accumulation of iodide could be detected in the gastric wall. The biological significance of this gastric iodide handling could not however, be discovered. A practical

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consequence that came from this knowledge of iodide accumulation in gastric contents was the assumption of safety measures when handling vomit from patients receiving radioiodine therapy. The accumulation of iodide in the gastric wall and juice is also suspected of being responsible for the elevated incidence of, and mortality in, gastric cancer after ^{131}I-therapy (Hall *et al.*, 1992; Holm *et al.*, 1991).

Studies on bovines showed a recirculation of iodide, and this was suggested to be an important iodide-conserving mechanism (Miller *et al.*, 1975b). The functional role of iodide secretion into the gastric lumen has, however, remained elusive.

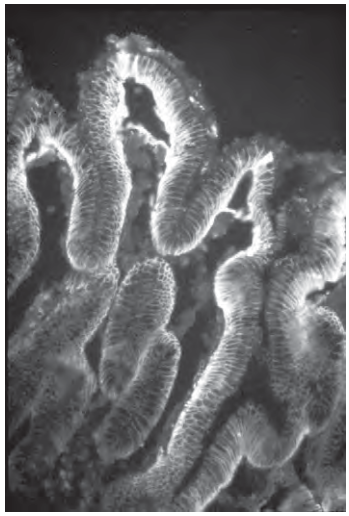
NIS Background

In the thyroid gland iodide is actively transported into the thyrocyte by the sodium iodide symporter (NIS). The transport of iodide against a gradient is powered by Na^+/K^+-ATPase, and competitively inhibited by perchlorate (see review by Carrasco, 1993). With the revelation of the complementary deoxyribonucleic acid (cDNA)-sequence of rat-NIS (Dai *et al.*, 1996), soon followed by the sequencing of human NIS (Smanik *et al.*, 1996), a new era of intensive iodide research started. NIS was also soon identified in the gastric wall and the cDNA-sequence of human gastric NIS was revealed (Spitzweg *et al.*, 1998).

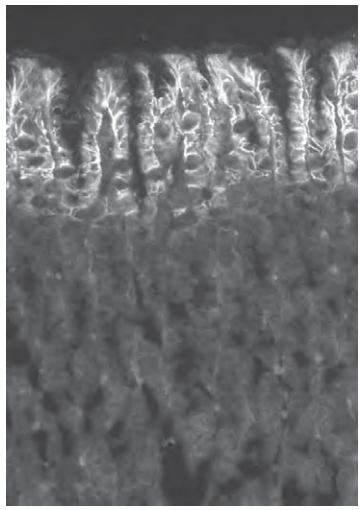
Gastric NIS Detection and Distribution

NIS protein is present in large amounts in the gastric mucosa, mainly located in the basolateral cell membranes of the epithelial surface cells. This has been demonstrated by immunohistochemistry with a polyclonal antiserum raised against human NIS in man (Vayre *et al.*, 1999), and with a polyclonal antiserum raised against rat-NIS in mouse, rat, guinea pig, pig and man (Josefsson *et al.*, 2002) (**Figure 22.1**). Expression of NIS was confirmed by demonstrating NIS messenger ribonucleic acid (mRNA) by *in situ* hybridization in mouse, rat and guinea pig (Josefsson *et al.*, 2002) (**Figure 22.2**), but the *in situ* probe used in these experiments unfortunately did not recognize NIS mRNA in porcine or human tissue. These findings are in accordance with the findings of Ajjan *et al.* (1998) who utilized southern blot and reverse transcriptase-polymerase chain reaction (RT-PCR) and found high levels (> 80% of thyroid level) of NIS mRNA in rat gastric mucosa.

NIS is located in the basolateral cell membranes of both the oxyntic and the pyloric portions of the gastric mucosa in rat, as well as in man (Josefsson *et al.*, 2002; Vayre *et al.*, 1999). In the rumen (*pars proventricularis*) of rat and mouse no NIS was found (Josefsson *et al.*, 2002), which is not surprising considering that this part of the rodent stomach is lined by squamous epithelium and not gastric glandular mucosa as in the rest of the stomach. Apart from the abundant presence of NIS in the surface epithelial cells, NIS-immunoreactivity within parietal cells has also been described in mouse, guinea pig and man (Josefsson *et al.*, 2002; Spitzweg *et al.*, 1999). These findings could not however, be confirmed by *in situ* hybridization (Josefsson *et al.*, 2002), and thus the presence of authentic NIS in parietal cells is strongly questioned.



(a)



(b)

Figure 22.1 NIS in gastric mucosa. Sections of gastric mucosa from (a) the pyloric region of man; and (b) the oxyntic region of rat. Sections were stained by immunohistochemistry using a polyclonal antiserum raised in rabbit against a BSA-conjugated peptide corresponding to rat-NIS eight C-terminal amino acids. The site of the antigen–antibody reaction was revealed by FITC-labeled pig anti-rabbit IgG. Staining is intense in the basolateral cell membranes of the epithelial surface cells of human (a) and rat gastric mucosa (b). Magnification a ×160 and b ×180.

Figure 22.2 NIS mRNA in rat gastric mucosa. Section of rat stomach oxyntic mucosa autoradiographically labeled for NIS mRNA by a 33-mer oligonucleotide probe complementary to rat thyroid NIS mRNA 570–602 and 3′-endtailed with ^{35}S-dATP. Intense labeling (black silver grains) is seen in the gastric surface epithelium. Magnification ×200.

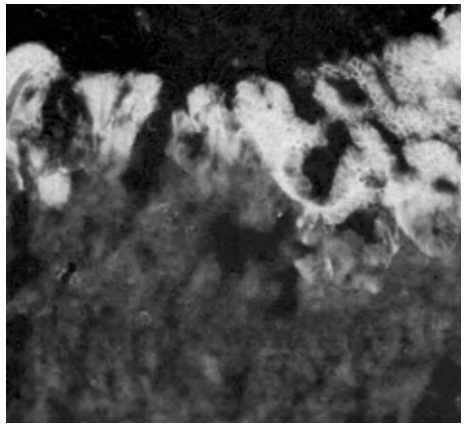


Figure 22.3 Gastric NIS in rat fetus. Section of oxyntic mucosa from a rat fetus at E19 stained by immunohistochemistry with a polyclonal antiserum raised against the eight C-terminal amino acids of rat-NIS. The site of the antigen–antibody reaction was revealed by FITC-labeled pig anti-rabbit IgG. Staining is intense in the basolateral cell membranes of the epithelial surface cells. Magnification ×200.

Gastric NIS during Development

The presence and distribution of NIS and NIS mRNA expression have been explored in the rat gastric mucosa and thyroid during embryonic development and throughout the neonatal period (postnatal day 0–13) (Josefsson and Ekblad, unpublished). Gastric NIS was detected by immunohistochemistry and NIS mRNA by *in situ* hybridization. Expression of NIS in the gastric mucosa already occurs at embryonic day 17 (E17), which coincides with the appearance of NIS protein and NIS mRNA within the thyroid (Josefsson and Ekblad, unpublished). At this time-point gastric NIS-immunoreactivity is intense and located in the basolateral cell membranes of the epithelial surface cells. The topographic distribution and staining intensity noted in gastric mucosa at E17 persist during the later part of embryonic development and also throughout the neonatal period (Figure 22.3). Thus, the presence and expression of gastric NIS in pre- and postnatal rats are identical to those of adult rats. This is in contrast to the neonatal versus adult expression of thyroidal NIS which, although located to the basolateral cell membranes of the follicular cells, shows a patchy distribution in neonatal rats. In adult rats NIS is evenly distributed throughout the thyroid.

Gastric Iodide Transport Mediated by NIS

In vivo

Gastric iodide transport has been studied earlier *in vivo* in e.g. dog, rat (Brown-Grant, 1961) and bovines (Miller *et al.*, 1975a). The conclusions reached included that iodide is readily transported from the bloodstream into the gastric lumen, but not in the opposite direction, and that this transport is inhibited by thiocyanate, and even more effectively by perchlorate. In a recent study ^{125}I accumulation in thyroid was measured after oral or intravenous administration, respectively. In both groups animals with or without pyloric ligation were included. Thyroid ^{125}I accumulation was at least of the same magnitude after oral administration without pyloric ligation as after intravenous administration, but virtually no accumulation of ^{125}I was seen in the thyroid after oral administration with pyloric ligation (Josefsson *et al.*, 2002) (Table 22.1). In the group with pyloric ligation receiving ^{125}I intravenously, ^{125}I was measured in the gastric contents and after 60 min the amount of ^{125}I present in gastric lavage fluid ranged from 8.5% to 16% of the total administered dose, with the higher values in the group with pyloric ligation (Josefsson *et al.*, 2002) (Table 22.1). In conclusion, these *in vivo* experiments support the concept that iodide is actively secreted into the gastric lumen but not, to any significant degree, absorbed through the gastric mucosa.

In vitro

To be able to study iodide transport across gastric mucosa with better-controlled premises we developed an Ussing-chamber *in vitro* model (Figure 22.4) (Josefsson *et al.*, 2006). In this model we demonstrated considerable iodide transport from the serosal to the mucosal side, which was linear over time, while transport from the mucosal to the serosal side was negligible (Figure 22.5). The iodide

Table 22.1 Iodide uptake (percentage of total administered dose) in rat after oral or intravenous administration

Administration	*Pyloric ligation*	*n*	*Thyroid*	*Blood (0.3 ml)*	*Gastric lavage*
Oral	No	3	3.5–4.2	0.35–0.38	
	Yes	4	≪0.5	0.004–0.2	
Intravenous	No	3	1.2–2.1	0.27–0.47	8.5–13
	Yes	3	1.1–2.7	0.31–0.54	11–16

Uptake of ^{125}I in the thyroid 1 h after oral or intravenous administration. Each route of administration was tested with and without pyloric ligation. After oral administration uptake was negligible with pyloric ligation. Values are ranges and expressed as a percentage of total administered dose.

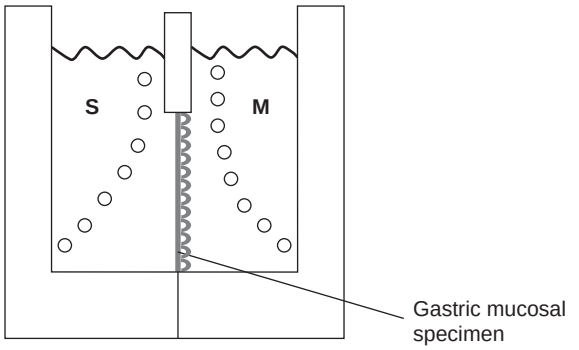


Figure 22.4 Schematic illustration of the Ussing-chamber. The chamber consists of two separate wells connected via an opening with a well-defined area (0.64 cm^2). Across the opening, the gastric mucosal specimen with the muscular layer stripped off is mounted. Both wells are filled with buffer solution and are continuously bubbled with carbogen (represented by small circles in the picture). The mounting of the specimen results in a polarized system with one serosal side (S) and one mucosal side (M). In order to measure transport over time, iodide is added to one side, and samples are then drawn from the other side at intervals.

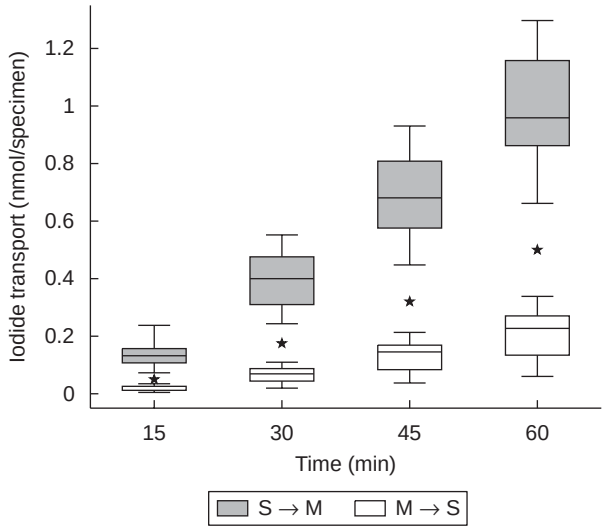


Figure 22.5 Direction of iodide transport across rat gastric mucosa in Ussing-chamber. Boxplots (medians, interquartile range and whiskers drawn to the extreme values) showing iodide transport from serosal to mucosal side (shadowed boxes, $n = 11$) and from mucosal to serosal side (open boxes, $n = 8$). Values are nanomole transported per specimen (0.64 cm^2) after 15, 30, 45 and 60 min. Initial iodide concentration was 0.02 mM. $^*P < 0.001$ at all time points.

transport from the serosal to the mucosal side was to a large extent, but not totally, inhibited by the selectively competitive NIS inhibitor perchlorate (Figure 22.6), indicating that NIS is responsible for this iodide transport. Further evidence supporting that NIS contributes in gastric iodide secretion is that transport was also attenuated by ouabain, an inhibitor of Na^+/K^+-ATPase (Figure 22.6).

Regulation of Gastric NIS

Thyroid NIS expression is primarily regulated by thyroid-stimulating hormone (TSH), but also by other factors, e.g., iodide and cytokines as described in a review by Dohan *et al.* (2003). However, TSH is unable to change the rate by which iodide is transported over gastric mucosa both *in vivo* (see review by Brown-Grant, 1961) and *in vitro* (Josefsson *et al.*, 2006). So far, no known regulators either of gastric NIS expression or gastric NIS activity have been identified. In our Ussing-chamber model, besides TSH, we also tested thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), histamine and the NO-donor S-nitroso-*N*-acetyl-D, L-penicillamine (SNAP), to investigate a possible neuroendocrine regulation of NIS activity, but none of these substances influenced the rate of gastric iodide secretion (Josefsson *et al.*, 2006). However, it must be emphasized that only acute regulatory effects can be studied in the Ussing-chamber *in vitro* model. The possibility of a neuroendocrine regulation of gastric NIS mRNA expression is still unexplored.

Thyroid NIS expression has been reported to be increased in fetuses in iodine-deficient rats (Schroder-van der Elst *et al.*, 2001), but no studies concerning the expression and regulation of gastric NIS during development have so far been performed.

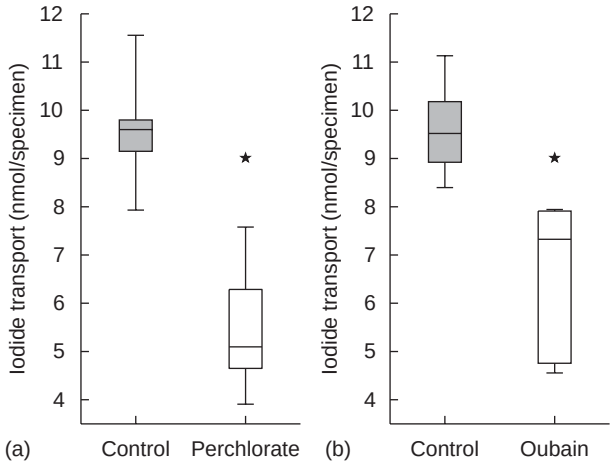


Figure 22.6 Attenuation of iodide transport in Ussing-chamber by perchlorate and ouabain. Rat gastric mucosa was tested. Boxplots (medians, interquartile range and whiskers drawn to the extreme values) showing iodide transport from the serosal to the mucosal side in rat gastric mucosa specimens in the presence of (a) perchlorate 20 mM ($n = 7$) compared to control ($n = 6$); or (b) ouabain 500 μM ($n = 5$) compared to control ($n = 5$). Initial iodide concentration was 0.2 mM. Values are nanomole transported per specimen (0.64 cm^2) after 60 min. $^*P < 0.01$ in a and b.

Functional Role of Gastric NIS

The presence of NIS in the gastric mucosa may serve several purposes. As NIS is abundantly expressed in the gastric mucosa of all studied mammals (Josefsson *et al.*, 2002), and also appears at the same gestational age in the embryonic development as thyroid NIS (unpublished observation by the authors, see section on "Gastric NIS during Development"), it is hard to believe that it is unimportant. The concept of recirculation as a means of iodide conservation, as previously mentioned, is only one possibility. One proposed hypothesis is that iodide acts as an antioxidant in the gastric lumen (Venturi and Venturi, 1999). Another possibility is that iodide has important antimicrobial effects in the gastric lumen (Majerus and Courtois, 1992). NIS can however, also transport other anions in addition to iodide, among which are nitrate (NO_3^-) (Wolff, 1998). The transport of NO_3^- is less efficient than that of iodide, but since plasma concentration of NO_3^- is normally much higher than that of iodide the total transport of NO_3^- may still be considerable. Studies on NIS transport of different anions have mostly been performed on thyroid-derived systems, like cells transfected with thyroid NIS or thyroid slices (see Eskandari *et al.*, 1997; Wolff, 1998 for reviews). Gastric NIS may have somewhat different transport properties, due to differences in post-translational modification, most probably divergent glycosylation (Tazebay *et al.*, 2000). NO_3^- is reduced to nitrite (NO_2^-) by bacterial enzymes and, in an acidic environment, then nonenzymatically reduced to nitric oxide (NO) (McKnight *et al.*, 1997; Weitzberg and Lundberg, 1998) – a powerful antimicrobial agent. Thus both iodide and NO_3^- may play important roles in our defense against microbes (Fite *et al.*, 2004). In addition, Fite *et al.* (2004) also indicate that the presence of iodide enhances the antimicrobial effect of NO. Interestingly, an entero-salivary recirculation of NO_3^- has been suggested by several groups (for an overview see Duncan *et al.*, 1997) and the salivary glands are, together with the thyroid, gastric mucosa and lactating mammary gland, the locations in which NIS is expressed in considerable amounts (Josefsson *et al.*, 2002; Spitzweg *et al.*, 1998).

Gastric Cancer and NIS

Gastric cancer is one of the most common neoplasms worldwide, and the diagnosis also carries a bad prognosis. Interestingly there are reports of gastric cancer being more prevalent in areas with iodine deficiency and possibly also with iodine excess (Venturi *et al.*, 2000). This indicates that the iodide secretion into the gastric lumen, mediated by NIS, may be an important factor in gastric carcinogenesis. In this context it is also interesting to note that NO_3^-, often suggested to be a risk factor for gastric cancer, is also transported by NIS, and that high levels of NO_3^- certainly would competitively reduce the iodide transport. A higher prevalence of thyroid disease (nontoxic goiter and autoimmune thyroid disease) in subjects with gastric cancer compared with matched controls has been reported (Kandemir *et al.*, 2005). A weakness in this report is that the authors do not provide any information on whether subjects with thyroid disease had received radioiodine therapy, which has previously been reported to elevate incidence of, as well as mortality in, gastric cancer (Hall *et al.*, 1992; Holm *et al.*, 1991).

Apart from the possible functional role of NIS-mediated iodide transport in gastric carcinogenesis, NIS expression is also interesting as a possible diagnostic tool for gastric cancer recurrence or metastasis, as indicated in a case report by Wu *et al.* (1984). On the other hand, Altorjay *et al.* (2007) found NIS expression to be absent or low in gastric carcinoma, and suggest that decreased NIS expression in gastric lesions could be used as a sign of malignancy. In the future it may be possible to use radioiodine accumulation by NIS for treatment of different types of cancer. To achieve this, ways to induce or enhance NIS expression in cancer cells must be explored. Gene transfer has been suggested as one means of inducing NIS expression (for a review see Dohan *et al.*, 2003) and chemical induction or enhancement of NIS expression by retinoic acid in cell lines has been reported in cell lines by Kogai *et al.* (2000).

Summary Points

- Iodide accumulation in gastric juice and within the gastric wall has been recognized since the middle of the last century.

- The sodium iodide-symporter (NIS) has been detected in gastric mucosa by immunohistochemistry, *in situ* hybridization and the combination of RT-PCR and southern blot.
- NIS is located in the basolateral cell membrane of the gastric mucosal surface cells.
- Gastric NIS is expressed in rats from E17 and abundantly expressed during the neonatal period.
- Iodide is actively transported from the bloodstream into the gastric lumen, but not in the opposite direction.
- Iodide secretion into the gastric lumen is mediated by NIS.
- The regulation of gastric NIS expression is still unknown.
- The physiological function of gastric NIS, as well as of gastric iodide transport, is poorly understood. Hypotheses include: antimicrobial effects of iodide, antioxidative effects of iodide, recirculation of iodide, and the transport of other anions such as NO_3^- by NIS.
- Gastric cancer, as well as thyroid disease, is more prevalent in areas of iodine deficiency.
- NIS expression might, in the future, be used in the diagnosis of gastric cancer metastasis or the absence of NIS expression as a sign of malignancy in gastric lesions.
- If NIS expression can be increased in cancer cells, i.e., by gene transfer or chemical induction, this could make radioiodine treatment possible not only in thyroid disease, but also in gastric cancer.

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