21

Cellular Iodine Transport: Body Distribution of the Human Sodium Iodide Symporter

Matthew J. Provenzano Department of Otolaryngology – Head and Neck Surgery, 200 Hawkins Drive, University of Iowa, Iowa City, IA 52242-1078, USA
Frederick Domann and Laura Hefley Department of Radiation Oncology, B180 Med Labs, The University of Iowa, Iowa City, IA 52242-1181, USA

Abstract

Iodine plays an essential role in human development and the normal physiology of adults. Hence, absence of this critical element can lead to a number of different disease states in life. Because of its centricity of normal physiology, the body has developed a complex system of iodine absorption, concentration, storage and delivery. This system utilizes a number of different organ systems and ensures that iodine is available to a developing fetus, a young child, or a grown adult. In addition to its role in human physiology, the body produces a number of iodine-containing compounds that it then utilizes in its constant fight against infectious diseases. In this way, iodine helps minimize the possibility of bacterial infection in the upper digestive tract and the eyes. In order to accomplish these tasks, the body makes use of a specialized ion transporter, the sodium iodine symporter, to deliver iodine to the proper organs. This chapter examines the distribution of the symporter throughout the body. Special attention is paid to its biological significance, structure and function. Each organ important to the iodine handling process is examined for evidence of expression of the symporter. Throughout the discussion, a number of tools and techniques important to molecular biology are considered to demonstrate how specific organs utilize iodine. Each technique is briefly explained to provide the reader with a better understanding of how current scientific studies contribute to the understanding of iodine use.

Abbreviations

cAMP	Cyclic adenosine monophosphate
DNA	Deoxyribonucleic acid
hNIS	Human sodium iodide symporter
I^-	Iodide
mRNA	Messenger RNA
Na^+	Sodium
NIS	Sodium iodide symporter
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
rNIS	Rat sodium iodide symporter
RT-PCR	Reverse transcription-polymerase chain reaction
TSH	Thyroid-stimulating hormone

Introduction

Iodine is essential for the human body. Failure to have proper amounts of this element during development or in adulthood can lead to a host of medical problems, including mental retardation, cardiac complications, metabolic disturbances and mental health illness. Illnesses resulting from lack of iodine are common and have been known for centuries. Congenital hypothyroidism, initially referred to as cretinism, was described in the eighteenth century. Likewise, the large goiters in iodine-deprived individuals are well described and not uncommon in many countries. Because of the potential consequences of not having the proper amount of iodine, the body possesses a number of mechanisms by which it can absorb, collect, concentrate and excrete iodine in the form of its monovalent anion iodide. This system encompasses a large number of organ systems and different physiological processes, all to ensure that iodine processing and utilization take place properly.

Humans ingest iodine through food. In many countries, iodine fortification, normally through iodized salt, ensures proper iodine intake. The ingested iodine is then absorbed into the bloodstream through the gut. Once absorbed, the major location of iodine storage and utilization is the thyroid. Iodine is transported into the thyroid from the

Comprehensive Handbook of Iodine
ISBN: 978-0-12-374135-6

bloodstream by a protein, the sodium iodide symporter (hereafter referred to as either the symporter or NIS). Definitions of some of the key terms used throughout this chapter are shown in Table 21.1.

In the thyroid gland, iodine plays perhaps its most important role through incorporation into the thyroid hormone precursor thyroglobulin. It is through the diverse actions of thyroid hormones that iodine becomes important in the regulation of a number of different physiologic systems. Here, also, the role of the symporter has been studied extensively. Both molecular biology techniques and imaging studies have been used to describe the role that NIS plays in thyroid physiology.

A second major organ of iodine uptake is the breast. Iodine is essential for the developing child. If iodine is unavailable during development, the child can develop congenital hypothyroidism. This disease, marked by mental retardation and numerous physical deformities, clearly demonstrates the critical role of iodine in early life. The mother provides adequate amounts of iodine to the developing child through breast milk, which helps in preventing the disease. Delivery of iodine through the milk is a continuation of the process that started when the child was *in utero*; the mother provides the fetus with iodine through the concentrating properties of the symporter located in the placenta. The presence of NIS within both breast tissue and the placenta ensures that the proper amount of iodine will be present during development.

Table 21.1 Definitions of common terms in iodine physiology and transport

Sodium: An element essential for human life. Sodium (symbol Na on the periodic table, it has atomic number 11 and a mass of 23 Da). Proteins that transport elements in and out of the cells often use sodium as a cotransporter molecule, thereby taking advantage of chemical gradients that exist within the body.

Iodine and iodide: Iodine is the pure form of the element (symbol I on the periodic table, it has atomic number 53 and a mass of 127 Da). Iodine describes the chemical state of the element when it is not an ion, when it usually exists in its pure form as I_2. Iodide is the ionized form of iodine found within the body. In this chemical state, the element exists as an ion (it has a negative charge of −1) and can participate in a number of chemical and biological processes. It is the substrate for the Na^+ I^- symporter defined below.

Symporter: A protein found at cell membranes that actively transports multiple molecules into a cell simultaneously. The prefix "sym" means "together" or "with"; the root word "porter" is derived from the word "transporter."

Sodium iodide symporter: A symporter that transports sodium and iodide simultaneously into a cell.

Notes: Knowledge of basic terms is essential to understanding iodine physiology and transport in the body. The Na^+I^- symporter actively transports sodium and iodide, the ion form of iodide, into the cell.

In addition to its role in human physiology, iodine is an integral part of a number of compounds important for fighting infectious diseases. Secretion of these compounds in the upper digestive tract and eyes helps ensure that those parts of the body constantly exposed to outside contamination remain free of bacterial infection. Loss of these iodine-containing protective compounds could place people at risk of bacterial infections. The presence of the symporter at these locations is central to providing the needed iodine for immunologic protection.

Methods to Detect NIS Expression

Determining the presence of the symporter throughout the body utilizes a number of molecular biology and nuclear medicine techniques (Figures 21.1 and 21.2). One method involves harvesting the ribonucleic acid (RNA) from the tissues and measuring the amount of NIS messenger RNA (mRNA). This mRNA is the result of transcription of the deoxyribonucleic acid (DNA) strand, RNA processing and eventually translation by the ribosomes to form the mature NIS protein. RNA can be used directly to measure

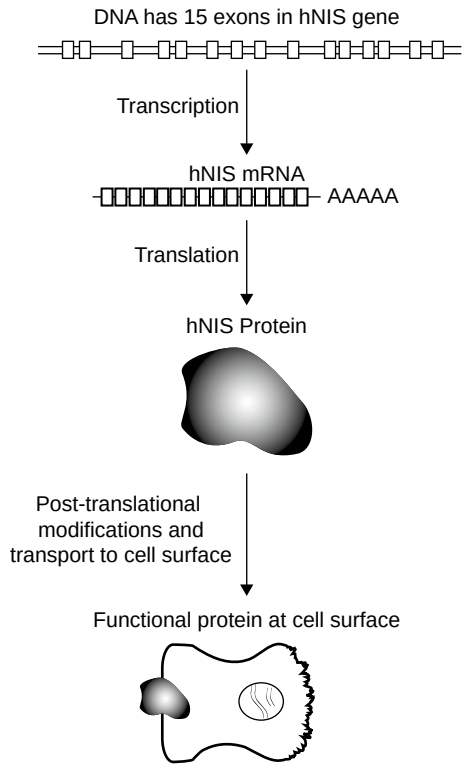

Figure 21.1 Placement of a functional sodium iodide symporter (NIS) at the cell's basolateral surface is a complex process involving a number of molecular biological steps. The gene is first translated into mRNA. The mRNA is then translated into a protein, which must then be properly folded, glycosylated and otherwise modified, and successfully trafficked to and inserted into the cell's basolateral plasma membrane.

NIS mRNA such as by northern blotting. Also, through the process of reverse transcription and a polymerase chain reaction (hereafter referred to as RT-PCR), a DNA strand identical to the RNA strand is formed and detected in a very sensitive assay. These RNA-based assays are two methods that can determine whether the symporter mRNA was present in a given tissue. Detection of symporter mRNA would indicate that the gene was being expressed.

Detection of the symporter protein can also take place through various means. In western blotting, proteins harvested from cells or tissues can be separated on a denaturing polyacylamide gel, transferred to membranes, and then probed with specific antibodies directed toward the symporter protein that can indicate whether the symporter was present in that specific tissue. These specific antibodies may also be utilized in a process called immunohistochemistry. In this method, the tissue remains whole and is sectioned into thin slices for easy study under a microscope. Treatment of this tissue with the antibody directed against the symporter then allows for the detection of the protein within the tissue slice. A final method of determining symporter expression and iodine uptake makes use of the fact that some iodine isotopes are radioactive. The location of these radioactive isotopes can be determined by using cameras that detect iodine's radioactive emissions. This allows for the visualization of the entire body to determine which sites actively take up iodine. However, it is specific to iodine and not the symporter. Therefore, it provides evidence as to where NIS *could* be located and does not exclude the possibility that iodine could be transported by a different protein.

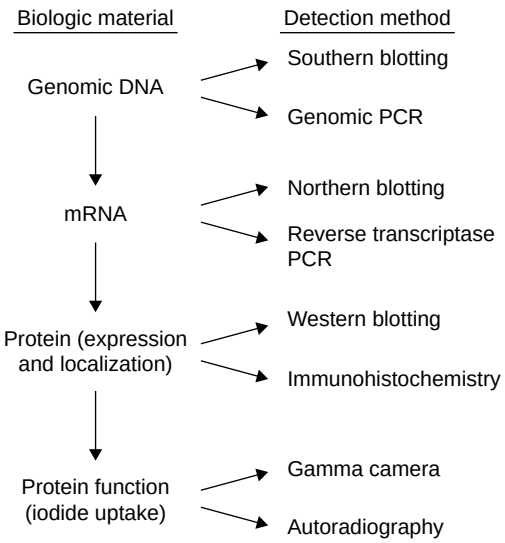

Figure 21.2 Detection strategies for the sodium iodide symporter (NIS) at each of the major biological steps along its synthesis and trafficking. Gene rearrangements, deletions, or amplifications can be measured at the level of genomic DNA by southern blotting or genomic PCR. Expression of the gene at the mRNA level can be detected by northern blotting or reverse transcriptase polymerase chain reaction (RT-PCR). Expression of the protein can be measured by western blotting or immunohistochemistry, the latter also being particularly useful for determining protein localization. Detection of a functional symporter can be determined by iodide uptake assays coupled with appropriate detection strategies, including autoradiography or gamma camera scintigraphy.

Using these methods, detection of the symporter in a number of tissues in the body has been possible. Symporter expression has been detected in both the thyroid and a number of different tissues using RT-PCR and northern blot (Spitzweg *et al.*, 1999). Many nonthyroidal tissues actively take up iodide; these include salivary glands, choroid plexus, ciliary body of the eye, gastric mucosa, placenta and lactating mammary glands (Dohan *et al.*, 2003). This chapter explores the various locations throughout the body where iodine is important. However, examination of the distribution of iodine uptake and utilization must begin by first examining the sodium iodine symporter.

The Sodium Iodide Symporter

An intrinsic membrane protein, the sodium iodide symporter, facilitates the active accumulation of iodide in a cell. Located on human chromosome 19, the gene is interspersed with 14 introns. Western blotting of the NIS protein shows a major band corresponding to a molecular weight of 97 kDa. Upon translation, the symporter then undergoes a number of post-translational modifications including glycosylation. Proper folding and transportation to the cell surface results in a protein that spans the plasma membrane 13 times. Perturbations in any of these steps can result in a nonfunctioning symporter. A previous study has demonstrated that high levels of NIS mRNA do not correlate with NIS activity in cultured cells (Kogai *et al.*, 2000). The reason for this speaks to the complexity of the symporter itself. NIS function depends not only on the post-translational modifications it undergoes, but also on the polarity of the cells and their organization (Dohan *et al.*, 2003; Kogai *et al.*, 2000). NIS expression and function were improved when the cells organized themselves into the follicles reminiscent of those found in the thyroid gland, instead of a normal monolayer of cultured cells. The complexity and size of the symporter have been demonstrated by experiments utilizing both the human sodium iodide symporter (hNIS) and that from other animals, such as rat NIS (rNIS). The hNIS is much larger and more complex than rNIS. Cells transfected with rNIS had higher levels of functioning symporter at the cell surface, as measured by iodine uptake, compared to those transfected with hNIS (Zhang *et al.*, 2005). The differing complexity of these two related proteins may contribute to the different levels of functional symporter.

Once present on the cell surface, the symporter works by cotransporting a negatively charged iodide molecule and a positively charged sodium ion to the cell (**Figure 21.3**).

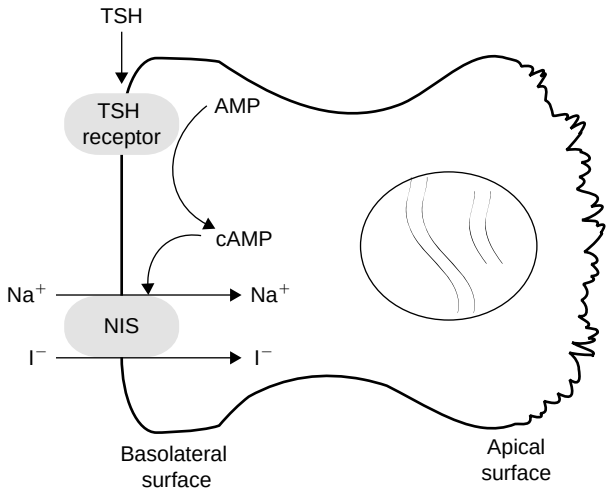

Figure 21.3 The symporter functions at the basolateral surface of the cell to bring iodide into it. Although a number of different hormones and molecules help regulate the sodium iodide symporter (NIS) expression, thyroid-stimulating hormone (TSH) is the most common regulator of the symporter. In this figure, TSH binds with its receptor, allowing for an increase in cAMP that in turn can power the symporter. Iodide, and two accompanying sodium ions, is transported into the cells through the function of the symporter.

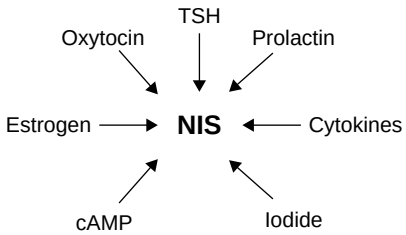

Figure 21.4 Regulation of the symporter occurs through a variety of hormones and molecules. This finding is consistent with its expression in diverse tissue types. NIS expression can be changed through the actions of thyroid-stimulating hormone (TSH), oxytocin, prolactin, estrogen, inflammatory cytokines, iodide, or cAMP levels.

NIS binds the sodium first followed by the iodide ion, which initiates a conformational change of the protein (Chung, 2002). The transport then takes place through an active, cyclic adenosine monophosphate (cAMP)-induced conformational change in the symporter. This transport mechanism in part utilizes a concentration gradient created by the ATP-dependent Na^+/K^+ exchange transporter located on the cell surface, which maintains a low intracellular concentration of sodium. Depending on the tissue type, iodine is then utilized in various biological processes, transported out of the cell, or organified into a protein/iodide molecule and stored for later use.

Complex mechanisms control NIS expression (Figure 21.4). Different tissue types often utilize different methods of controlling symporter expression. For example, thyroid-stimulating hormone (TSH) plays an important role in NIS expression in the thyroid, while hormones such as estrogen are important in NIS expression in the breast. These various means will be discussed in relationship to the various organs. NIS expression can also be affected – many times through unknown mechanisms – by various disease states. In various forms of thyroid and breast cancer, NIS expression is lost relative to the normal cells of origin of the tumor for as-yet unknown reasons.

Thyroid Gland

The expression of the sodium iodide symporter is perhaps nowhere more important than in the thyroid gland. A complete review of the physiological importance of the thyroid is beyond the scope of this chapter. It is sufficient to say that the symporter provides the iodine needed for normal thyroid function. Once the symporter has been trafficked to the basolateral surface of the thyrocyte, it can transport iodine from the blood into the cell. Once inside the cells, iodine is transported to the apical membrane where it is organified through attachment to a tyrosine residue and incorporated into the thyroid hormone thyroglobulin. The thyroglobulin is then stored inside thyroid follicles as colloid, to be released into the bloodstream as thyroid hormones (thyroxine and triiodothyronine) via TSH stimulation.

TSH stimulates expression of NIS and drives its localization to the thyroid cell basolateral membrane (Dohan *et al.*, 2003). The importance of TSH stimulation in NIS regulation has been demonstrated by studies showing an absence of iodine uptake after suppression of TSH (Martino and Pinchera, 2000). TSH performs this function through activation of adenylate cyclase and increases in cAMP. Following transcription and translation, the protein is then transported to the cell surface. However, evidence suggests that localization of a functional symporter to the cell surface is a highly complex and regulated process which depends on cellular organization and cellular polarity (Kogai *et al.*, 2000). All of these factors are important in the process of determining the subcellular localization of the symporter, with some evidence suggesting that NIS may be absent from the cell surface but still present within membrane vesicles within the cell (Kaminsky *et al.*, 1994). Iodine can also help regulate NIS expression. This mechanism has been known for many years, and has been described as the Wolff-Chaikoff effect. Thyroid uptake of iodine is blocked through administration of high doses of the element. Although the exact details of this mechanism remain unknown, evidence suggests that high levels of iodine in the blood may inhibit TSH-mediated mechanisms of NIS expression (Panneels *et al.*, 1994). Blocking of TSH-regulated symporter expression can also occur through the action of various cytokines. Finally, estrogen may serve as another regulator of symporter levels. This

mechanism, to be discussed in greater detail later in the chapter, has been born out by the observation that there may be a connection between estrogen levels and susceptibility to goiters (Furlanetto *et al.*, 1999).

There is overwhelming evidence of the symporter in the thyroid. As early as the 1920s, the physician Plummer had observed that iodine was important to thyroid function. A further work has demonstrated that thyroid cells contain 20–40-fold higher intracellular concentrations of iodide than in the plasma (Carrasco, 1993). A number of studies have demonstrated the presence of NIS mRNA and NIS protein within the thyroid (Castro *et al.*, 1999; Dohan *et al.*, 2003). The presence of the symporter has been further confirmed through a host of imaging studies that have demonstrated the thyroid's ability to take up radioactive iodine. This is possible because the symporter can transport noniodine molecules into the cell. The affinity of NIS for several halides and pseudohalides enables the uptake of ^{99m}Tc-pertechnetate and ^{188}Re-perrhenate (Kotzerke *et al.*, 1998; Lin *et al.*, 2000). NIS-mediated uptake can also be competitively inhibited by the thiocyanate and perchlorate anions, the latter being of particular interest to environmental health science.

This unique ability of NIS to concentrate iodide and other ions has been utilized clinically in thyroid imaging and treatment of hyperthyroidism and thyroid cancer. Administration and detection of certain iodine isotopes can help determine whether the thyroid is taking up too much or too little iodine. These findings can often be suggestive of a thyroid malignancy. The presence of symporter in the thyroid gland also allows for the delivery of high doses of radioactive iodine almost exclusively to the thyroid, in order to ablate the thyroid tissue. This technique may be employed when a patient has hyperthyroidism or in order to kill malignant cells. Both the imaging and radioablative techniques make thorough use of the unique properties and location of the symporter in the thyroid gland.

Mammary Gland

Although the symporter's highest levels of expression occur in the thyroid gland, it is also detectable in a number of other tissues and organs (**Table 21.2**). Given the importance of proper thyroid function in human development, it is not surprising that the symporter would be located within the breast tissue, thereby allowing for delivery of iodine into breast milk for the baby's consumption. Iodine concentration in the breast milk also serves the purpose of providing antimicrobial protection. Iodine can be converted into a reactive compound with antimicrobial properties through the action of peroxidase enzymes (Geiszt *et al.*, 2003). This mechanism also confers antimicrobial properties to saliva and tears. These compounds are then secreted into the breast milk and protect the baby from infection.

Table 21.2 Major sites of sodium iodide symporter expression and iodide uptake in the human body

Thyroid
Lactating breast
Placenta
Gastric mucosa
Colonic mucosa
Parotid gland
Minor salivary glands
Lacrimal glands

Notes: The sodium iodide symporter plays an important role in a number of organs. In all of these organs, the symporter provides iodide for essential physiological processes. In addition, the regulation of the symporter is better understood in these organs.

As with the thyroid, molecular biology techniques have demonstrated that the symporter is responsible for the previously known iodine-concentrating ability of breast tissue. Detection of NIS mRNA in lactating breast tissue has shown that the gene is transcribed in this tissue (Perron *et al.*, 2001). Additional studies examining protein levels through immunohistochemistry, as well as imaging studies to detect iodine uptake, have demonstrated the presence of the symporter within breast tissue (Tazebay *et al.*, 2000).

NIS expression in breast tissue exclusively during lactation points to an estrogen-mediated mechanism of control. Suckling after birth can induce NIS expression, with additional studies demonstrating that the administration of hormones such as estrogen, prolactin and oxytocin also induce symporter expression (Wapnir *et al.*, 2004; Tazebay *et al.*, 2000). As in the thyroid, regulation of NIS expression in breast tissue is most likely a multifactorial process. Symporter expression can also be controlled through all-*trans*-retinoic acid. However, this mechanism depends on the presence of estrogen receptors (Alotaibi *et al.*, 2006).

Placenta

The presence of the symporter in placenta tissue highlights the importance of iodine during development. The presence of the symporter allows for the concentration of iodine by the placenta and delivery to the fetus. In this manner, the developing fetus has the iodine needed for use in thyroid gland and thyroid hormone production. Detection of symporter mRNA and protein through real-time RT-PCR and immunohistochemistry staining has demonstrated its presence in the placenta (Mitchell *et al.*, 2001; Di Cosmo *et al.*, 2006). Mechanisms controlling NIS expression in the placenta are not as well-understood as in the thyroid or breast. However, it appears that the placenta and thyroid may share some regulatory mechanisms for symporter expression. In the thyroid, the gene *pax8* is expressed and aids in TSH-mediated changes in the expression of other genes, such as the symporter. Evidence now suggests that *pax8* may also help regulate NIS

expression in the placenta (Ferretti *et al.*, 2005). However, the roles that pregnancy-exclusive hormones play in placental NIS expression remains to be described.

NIS Expression in the Stomach and Kidney

Given the importance of iodine in both human development and normal physiology, it would seem obvious that the symporter plays an important role in iodine absorption and excretion. Ingested iodine is primarily absorbed into the bloodstream through the duodenum – the upper portion of the small intestine – using a non-NIS mechanism. While transport of iodine into the blood would be expected, a number of additional studies have demonstrated iodine being transported from the bloodstream back into the lumen of the gut (Josefsson *et al.*, 2002). These findings correspond with a number of additional imaging studies, in both humans and animals, which have demonstrated iodine-concentrating properties in the digestive tract. They also correlate with evidence of the symporter expression in the gastric mucosa (Kotani *et al.*, 1998; Vayre *et al.*, 1999). As in the thyroid, the symporter is located along the basolateral surface of the cells. The exact function of iodine secretion *into* the gastrointestinal tract and *out of* the blood remains to be completely understood. Some have hypothesized that this may be part of a thyroid/gastric system to control circulating levels of iodine (Josefsson *et al.*, 2006), which would appear consistent with the previously described Wolff–Chaikoff phenomenon whereby circulating levels of iodine affect thyroid function and growth. Still others have posited that the reason for iodine secretion into the stomach may rest with iodine's potential antimicrobial properties (Spitzweg *et al.*, 1999). The control of NIS expression in the gut also appears to be distinct from other NIS-regulating mechanisms found elsewhere in the body, with some work demonstrating that TSH has no effect on NIS expression in the gut. Nor does it appear that regulatory molecules important to other gastric functions play a role in symporter expression in the gut (Josefsson *et al.*, 2006).

Blood iodine levels can also be controlled through excretion by the kidneys. Prior to detecting the symporter in kidney tissue, it has been known that iodine is accumulated and secreted in the kidney (Katz *et al.*, 1975). However, given the diverse filtering and secretion mechanisms found within the kidney, it was previously unknown whether NIS played an important role in this process. Examination of mRNA levels, western blotting to detect NIS protein and also immunohistochemistry of kidney tissue, have all revealed the presence of the symporter in this organ (Spitzweg *et al.*, 2001). These findings were then confirmed and extended by studies demonstrating iodine uptake by the kidneys. Aside from simply controlling the level of iodine circulating in the blood, symporter-mediated iodine concentration within the kidney may serve an additional purpose. Here, also, iodine and various compounds containing the element, such as iodolactones and α-iodo-hexadecanal, may play a role in kidney physiology (Dugrillon, 1996; Panneels *et al.*, 1994). Despite the symporter's importance in this organ, the regulatory mechanism underlying its expression in the kidney remains to be described.

Salivary and Lacrimal Glands

Areas such as the eye and the mouth are repeatedly exposed to infectious organisms. The fact that these areas are not frequent victims of infection speaks to a complex system of immunological protection in these areas. These tissues employ not only antibodies, but also the use of small molecules with antimicrobial properties. Iodine and iodine-containing compounds likely play an important role in protecting the body against infection. As has been discussed previously, through the action of various enzymes iodine can form a number of active compounds important for fighting disease. In the presence of a peroxidase such as lactoperoxidase, and hydrogen peroxide, iodide is activated to hypoiodous acid (HOI), which is a potent antimicrobial. In addition, unincorporated iodine itself is an important disinfecting agent.

Studies employing immunohistochemistry on tissues from salivary and lacrimal glands have demonstrated the presence of the symporter (Spitzweg *et al.*, 1999; Jhiang *et al.*, 1998). To date, there appear to be no iodine uptake studies in lacrimal tissue. In addition, the mechanism controlling NIS expression there remains to be understood. Given the importance of having proper immunological defense of these areas, it is reasonable to hypothesize that the symporter may be constitutively expressed. It is also possible that in the salivary and lacrimal glands, symporter expression falls under the control of inflammatory cytokines. Such a system would seem consistent with the antimicrobial function iodine appears to be playing in these tissues.

Other Tissues

A number of additional experiments have demonstrated NIS expression in various tissues throughout the body. A complete list of these tissues can be found in **Table 21.3**. This list is diverse, ranging from the pancreas, ovary, colon, heart and lung, to the adrenal and pituitary glands. In some instances, such as with the ovary and colon, the literature contains conflicting evidence of NIS expression (Spitzweg *et al.*, 1998; Perron *et al.*, 2001; Jhiang *et al.*, 1998; Tazebay *et al.*, 2000; Ajjan *et al.*, 1998; Smanik *et al.*, 1997). Evidence of symporter expression in thyroid and breast tissues ranges from detection of mRNA

Table 21.3 Minor sites of sodium iodide symporter expression and iodide uptake in the human body

Choroid plexus
Kidneys
Parotid
Thymus
Skin
Pituitary gland
Pancreas
Testis
Prostate
Adrenal gland
Lung
Heart
Nasopharyngeal mucosa
Extraocular muscles
Ovary

Notes: In addition to playing a prominent role in many organs, the sodium iodide symporter can also be found in a wide variety of other organs. In most of these locations, the symporter's function and regulation are unknown.

to protein detection and iodine uptake. Despite this, little evidence exists for many of these organs as to the regulation and function of the symporter.

Conclusion

Iodine plays an important role in human physiology, performing functions such as hormone synthesis as found in the thyroid, antimicrobial function as demonstrated in the breast and salivary glands, or its possible role in cellular physiology as hypothesized in the kidney. The sodium iodine symporter is central to regulating iodine uptake. Experiments examining mRNA levels, protein expression, and iodine uptake have demonstrated its presence in a host of organs and tissues. Much is already known of NIS function and regulation in organs such as the thyroid and breast. However, NIS expression in many parts of the body remains to be completely understood. Future experiments will help in better understanding the mechanism behind NIS regulation. Manipulation of NIS expression could aid in treating various diseases such as thyroid cancer or drug-resistant bacterial infections.

Summary Points

- Iodine is essential for human life. Failure to have proper amounts of this element during development and throughout life can lead to a number of disease states.
- The sodium iodide symporter transports iodine into the cell.
- The symporter is a large complex protein that is dependent on proper protein folding, posttranslational modifications, protein trafficking, cellular polarity and cellular organization for its function.
- The symporter transports an iodide ion into the cell through an active process using sodium ions as cotransport molecules.
- The symporter is expressed in numerous organs of the body including the thyroid, stomach, breast, placenta, salivary glands and eye.
- The mechanisms controlling expression of the symporter are often tissue-dependent and rely on a number of different proteins and hormones.
- Disease states such as cancer can change the expression of the symporter.

References

Ajjan, R.A., Kamaruddin, N.A., Crisp, M., Watson, P.F., Ludgate, M. and Weetman, A.P. (1998). Clin. Endocrinol. (Oxf.) 49, 517–523.

Alotaibi, H., Yaman, E.C., Demirpence, E. and Tazebay, U.H. (2006). Biochem. Biophys. Res. Commun. 345, 1487–1496.

Carrasco, N. (1993). Biochim. Biophys. Acta 1154, 65–82.

Castro, M.R., Bergert, E.R., Beito, T.G., Mciver, B., Goellner, J.R. and Morris, J.C. (1999). J. Clin. Endocrinol. Metab. 84, 2957–2962.

Chung, J.K. (2002). J. Nucl. Med. 43, 1188–1200.

Di Cosmo, C., Fanelli, G., Tonacchera, M., Ferrarini, E., Dimida, A., Agretti, P., De Marco, G., Vitti, P., Pinchera, A., Bevilacqua, G., Naccarato, A.G. and Viacava, P. (2006). Clin. Endocrinol. (Oxf.) 65, 544–548.

Dohan, O., De La Vieja, A., Paroder, V., Riedel, C., Artani, M., Reed, M., Ginter, C.S. and Carrasco, N. (2003). Endocrinol. Rev. 24, 48–77.

Dugrillon, A. (1996). Exp. Clin. Endocrinol. Diab. 104 (Suppl 4), 41–45.

Ferretti, E., Arturi, F., Mattei, T., Scipioni, A., Tell, G., Tosi, E., Presta, I., Morisi, R., Lacroix, L., Gulino, A., Russo, D., Damante, G. and Filetti, S. (2005). Endocrinology 146, 4009–4015.

Furlanetto, T.W., Nguyen, L.Q. and Jameson, J.L. (1999). Endocrinology 140, 5705–5711.

Geiszt, M., Witta, J., Baffi, J., Lekstrom, K. and Leto, T.L. (2003). Faseb. J. 17, 1502–1504.

Jhiang, S.M., Cho, J.Y., Ryu, K.Y., Deyoung, B.R., Smanik, P.A., Mcgaughy, V.R., Fischer, A.H. and Mazzaferri, E.L. (1998). Endocrinology 139, 4416–4419.

Josefsson, M., Evilevitch, L., Westrom, B., Grunditz, T. and Ekblad, E. (2006). Exp. Biol. Med. (Maywood) 231, 277–281.

Josefsson, M., Grunditz, T., Ohlsson, T. and Ekblad, E. (2002). Acta Physiol. Scand. 175, 129–137.

Kaminsky, S.M., Levy, O., Salvador, C., Dai, G. and Carrasco, N. (1994). Proc. Natl. Acad. Sci. USA 91, 3789–3793.

Katz, A.I., Emmanouel, D.S. and Lindheimer, M.D. (1975). Nephron 15, 223–249.

Kogai, T., Curcio, F., Hyman, S., Cornford, E.M., Brent, G.A. and Hershman, J.M. (2000). J. Endocrinol. 167, 125–135.

Kotani, T., Ogata, Y., Yamamoto, I., Aratake, Y., Kawano, J.I., Suganuma, T. and Ohtaki, S. (1998). Clin. Immunol. Immunopathol. 89, 271–278.

Kotzerke, J., Fenchel, S., Guhlmann, A., Stabin, M., Rentschler, M., Knapp, F.F., Jr. and Reske, S.N. (1998). Nucl. Med. Commun. 19, 795–801.

Lin, W.Y., Hsieh, J.F., Tsai, S.C., Yen, T.C., Wang, S.J. and Knapp, F.F., Jr. (2000). Nucl. Med. Biol. 27, 83–87.

Martino, E.B.L. and Pinchera, A. (2000). Central hypothyroidism. In: (ed U.R. Braverman Le), *The Thyroid: A Fundamental and Clinical Text.* 8th edn., Lippincott, Philadelphia, PA.

Mitchell, A.M., Manley, S.W., Morris, J.C., Powell, K.A., Bergert, E.R. and Mortimer, R.H. (2001). Placenta 22, 256–258.

Panneels, V., Van Sande, J., Van Den Bergen, H., Jacoby, C., Braekman, J.C., Dumont, J.E. and Boeynaems, J.M. (1994). Mol. Cell. Endocrinol. 106, 41–50.

Perron, B., Rodriguez, A.M., Leblanc, G. and Pourcher, T. (2001). J. Endocrinol. 170, 185–196.

Smanik, P.A., Ryu, K.Y., Theil, K.S., Mazzaferri, E.L. and Jhiang, S.M. (1997). Endocrinology 138, 3555–3558.

Spitzweg, C., Dutton, C.M., Castro, M.R., Bergert, E.R., Goellner, J.R., Heufelder, A.E. and Morris, J.C. (2001). Kidney Int. 59, 1013–1023.

Spitzweg, C., Joba, W., Eisenmenger, W. and Heufelder, A.E. (1998). J. Clin. Endocrinol. Metab. 83, 1746–1751.

Spitzweg, C., Joba, W., Schriever, K., Goellner, J.R., Morris, J.C. and Heufelder, A.E. (1999). J. Clin. Endocrinol. Metab. 84, 4178–4184.

Tazebay, U.H., Wapnir, I.L., Levy, O., Dohan, O., Zuckier, L.S., Zhao, Q.H., Deng, H.F., Amenta, P.S., Fineberg, S., Pestell, R.G. and Carrasco, N. (2000). Nat. Med. 6, 871–878.

Vayre, L., Sabourin, J.C., Caillou, B., Ducreux, M., Schlumberger, M. and Bidart, J.M. (1999). Eur. J. Endocrinol. 141, 382–386.

Wapnir, I.L., Goris, M., Yudd, A., Dohan, O., Adelman, D., Nowels, K. and Carrasco, N. (2004). Clin. Cancer Res. 10, 4294–4302.

Zhang, Z., Liu, Y.Y. and Jhiang, S.M. (2005). J. Clin. Endocrinol. Metab. 90, 6131–6140.