

# Anion Selectivity by the Sodium Iodide Symporter

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The iodide transporter of the thyroid (NIS) has been cloned by the group of Carrasco. The NIS-mediated transport was studied by electrophysiological methods in NIS-expressing *Xenopus* oocytes. Using this method, the anion selectivity of NIS was different from that previously reported for thyroid cells, whereas perchlorate and perrhenate were found not transported. In this study we compared the properties of human NIS, stably transfected in COS-7 cells to those of the transport in a thyroid cell line, the FRTL5 cells, by measuring the trans-

port directly. We measured the uptake of  $^{125}\text{I}^-$ ,  $^{186}\text{ReO}_4^-$ , and  $^{99\text{m}}\text{TcO}_4^-$  and studied the effect on it of known competing anions, i.e.  $\text{ClO}_4^-$ ,  $\text{SCN}^-$ ,  $\text{ClO}_3^-$ ,  $\text{ReO}_4^-$ , and  $\text{Br}^-$ . We conclude that the properties of the NIS transporter account by themselves for the properties of the thyroid iodide transporter as described previously in thyroid slices. The order of affinity was:  $\text{ClO}_4^- > \text{ReO}_4^- > \text{I}^- \geq \text{SCN}^- > \text{ClO}_3^- > \text{Br}^-$ . NIS is also inhibited by dysidenin (as in dog thyroid). (*Endocrinology* 144: 247–252, 2003)

THE TRANSPORT SYSTEM, which concentrates iodide in the thyroid, has been well characterized during the 1960s and 1970s. It operates against an electrical gradient at the basal membrane of the thyrocyte and is driven by an inward  $\text{Na}^+$  gradient maintained by the  $\text{Na}^+/\text{K}^+$  ATPase (1–4). The latter gradient depends on the ATP generated by mitochondrial and glycolytic metabolism (5). The fact that concentration of iodide in the saliva was also suppressed in cases of thyroid iodide-trapping defects suggested that the same system operates in other cells such as salivary gland and gastric mucosa (6).

An  $\text{Na}^+/\text{I}^-$  symporter (NIS) has been cloned by Dai *et al.* (7) using expression cloning in *Xenopus* oocytes and radioiodide uptake as an index. The specific expression of this symporter in thyroid and other iodide-concentrating cells and the observation of inactivating mutations in cases of iodide-trapping defects demonstrated its role in specific iodide transport (8). The mechanism of NIS-mediated transport has been studied by electrophysiological methods in NIS-expressing *Xenopus* oocytes using the fact that the symport of two  $\text{Na}^+$  and one  $\text{I}^-$  generates an easily measurable current. Using this method, the anion selectivity of the NIS showed the following order of affinity:  $\text{I}^- > \text{ClO}_3^- > \text{SCN}^- > \text{Br}^-$ . The anions perchlorate and perrhenate did not elicit any current, and it was suggested that these oxyanions were not transported (9). Similar results were obtained by patch clamping in NIS-expressing Chinese hamster ovary (CHO) cells and FRTL5 cells (10, 11). This raises a problem because these ions have been previously found to be concentrated by thyroid preparations *in vitro* (1) and for perchlorate *in vivo* (12–15). Moreover, it has recently been shown that perrhenate leaking from devices used in the treatment of aortic stenoses or

used as an alternative to iodine-131 for treatment of breast tumors is concentrated in the thyroid and stomach (16, 17). Finally, pertechnetate  $^{99\text{m}}\text{TcO}_4^-$ , which has a similar structure as perchlorate, has been an important imaging tool used for investigating thyroid uptake in nuclear medicine for a long time. The order of selectivities of the thyroid-trapping system:  $\text{ClO}_4^- > \text{ReO}_4^- > \text{SCN}^- > \text{I}^- > \text{Br}^-$  (18) is different from what was observed electrophysiologically.

Several hypotheses could explain these discrepancies, such as the existence of other transporters or complementary proteins in the thyroid or, more simply, an electroneutral mode of transport of  $\text{ClO}_4^-$  and  $\text{ReO}_4^-$  by the same symporter (19). To clarify whether NIS promotes transport of the oxyanions, we compared their uptake in FRTL5 thyroid cells and in COS-7 cells expressing stably high levels of NIS. This cell line had been generated previously in this laboratory (20).

## Materials and Methods

### Cell culture and reagents

COS-7 cells were transfected with the wild-type human NIS cDNA. Stable cell lines were selected by resistance to geneticin, and one clone, COS NIS-6 with a large capacity to accumulate iodide, was selected (20) and used in this study. A total of 250,000 COS NIS-6 cells were plated in 35-mm-diameter dishes and cultured in DMEM supplemented with 10% fetal bovine serum, 1 mM Na pyruvate, 100 IU/ml penicillin, 100  $\mu\text{g}/\text{ml}$  streptomycin, and 2.5  $\mu\text{g}/\text{ml}$  Fungizone. The cells were used the next day. FRTL5 were cultured in Coon's modified Ham's F12 medium (Life Technologies, Inc., Rockville, MD) supplemented with 5% calf serum, transferrin (5  $\mu\text{g}/\text{ml}$ ), insulin (5  $\mu\text{g}/\text{ml}$ ), bovine TSH (1 mU/ml, Sigma, St. Louis, MO), 100 IU/ml penicillin, 100  $\mu\text{g}/\text{ml}$  streptomycin, and 2.5  $\mu\text{g}/\text{ml}$  Fungizone. The cells were used after 2 d.

### Measurement of tracer uptake

The cells were rinsed with 1 ml Krebs-Ringer HEPES (KRH) buffer ( $\text{NaCl}$ , 124 mM;  $\text{KCl}$ , 5 mM;  $\text{MgSO}_4$ , 1.25 mM;  $\text{CaCl}_2$ , 1.45 mM;  $\text{KH}_2\text{PO}_4$ , 1.25 mM; HEPES, 25 mM, pH 7.4; glucose, 8 mM; BSA, 0.5 g/liter) and preincubated for 30 min in this buffer at 37 C. The medium was then

Abbreviations: KRH, Krebs-Ringer HEPES; NIS, iodide transporter of the thyroid; RU, relative uptake.

removed and replaced by fresh buffer containing the tracer (carrier-free Na  $^{125}\text{I}$ ,  $^{186}\text{Re}$  Na perrhenate, or  $^{99\text{m}}\text{Tc}$  Na pertechnetate), the agent under study, and 1 mM Na perchlorate or not. Methylmercaptoimidazole (0.1 mM) was used to block iodide organification in FRTL5 cells and therefore also with the COS NIS-6 cells. At the end of the incubation, the medium was discarded. The cells were rapidly rinsed twice with 1 ml cold PBS, dissolved in 1 ml 1 M NaOH, and counted. The uptake was expressed as the ratio of the radioactivity in the cells incubated without perchlorate to the radioactivity in cells incubated with perchlorate (relative uptake, RU). The RU in wild-type COS-7 cells was equal to one with the three tracers.

### Measurement of tracer efflux

A total of 500,000 cells were seeded in 6-cm-diameter dishes and grown for 24 h in the case of COS NIS-6 cells or 48 h in the case of FRTL5 cells, in their respective culture medium. The cells were then rinsed and incubated under slight agitation in KRH medium supplemented with  $10^{-7}$  M KI,  $10^{-4}$  M methimazole, and 1  $\mu\text{Ci}/\text{ml}$   $^{125}\text{I}$  iodide. After 1 h, the cells were rinsed with KRH at 37°C and then incubated with fresh medium for 60 min still under slight agitation. Fifty microliters of medium, out of 4 ml at the start, were withdrawn at 2, 4, 6, 10, 15, 30, and 60 min, respectively, and counted. At the end of the incubation, the cells were rinsed twice with KRH medium kept on ice. The cells were then dissolved in 1 M NaOH and counted. The efflux was expressed in percent of the total radioactivity taken up by the cells (cells + medium + serial aliquots).

$^{125}\text{I}$  as NaI (>0.6 TBq/mg iodide, >15 Ci/mg iodide) was purchased from Amersham Pharmacia Biotech UK Ltd., Little Chalfont, UK).  $^{186}\text{Re}$  as sodium perrhenate (> 29.6 GBq  $^{186}\text{Re}/\text{mg}$  perrhenate was from Mallinckrodt Nuclear Medicine (Tyco Healthcare, Mechelen, Belgium), and  $^{99\text{m}}\text{Tc}$  as Na Pertechnetate was provided to us by the Medical School hospital. It was prepared daily, carrier free, from a  $^{99\text{m}}\text{Tc}$  generator (ultra technecow, Mallinckrodt Nuclear Medicine). We used between 1 and 2  $\mu\text{Ci}$  ( $3.7\text{--}7.4 \times 10^4$  Bq) tracer per dish (1 ml medium). All the experiments were performed three times or more (3–10 times) except for  $^{186}\text{Re}$ , for which some were performed twice, which were in close agreement. The figures illustrate one representative experiment as means  $\pm$  SD. The duplicates (or triplicates) within one experiment are so close that we did not draw the SD on the figure.

### Results

The kinetics of  $^{125}\text{I}$  iodide,  $^{99\text{m}}\text{Tc}$  pertechnetate, and  $^{186}\text{Re}$  perrhenate uptakes were studied in COS NIS-6 and FRTL5 cells. In both cell lines, a rapid uptake was observed for all three tracers. At 5 min, the percentage of total radioactivity taken up by the cells was  $\pm 65\%$  for  $^{125}\text{I}^-$ ,  $\pm 80\%$  for  $^{99\text{m}}\text{TcO}_4^-$ , and  $^{186}\text{ReO}_4^-$  in COS NIS-6 cells and between 85% and 90%, regardless of the nature of the tracer in FRTL5 cells. A more rapid uptake in the FRTL5 cells was consistently observed in three independent experiments performed with each cell line. The equilibrium was reached after around 1 h, with often a slight decrease of the RU afterward (Fig. 1). Similarly, when the efflux of  $^{125}\text{I}^-$  from prelabeled cells was measured after washing the cells, it was faster in FRTL5 cells (half-efflux 3 min, complete 15 min) than in the COS NIS-6 cells (half-efflux 5 min, complete 30 min) (data not shown). When the uptakes of the three tracers were compared in the same experiment, the RU was highest for  $^{186}\text{Re}$  perrhenate, followed by  $^{99\text{m}}\text{Tc}$  pertechnetate and finally iodide, which was about half the value of  $^{186}\text{Re}$  perrhenate or less (Fig. 1). At concentrations well below the  $K_m$  of the transporter, this suggests a corresponding order of affinity.

For the study of transport competition, the uptake of

each of the three tracer anions was performed in both cell lines in the presence of increasing concentration of NaI,  $\text{NaClO}_4$ ,  $\text{NaReO}_4$ ,  $\text{NaSCN}$ ,  $\text{NaClO}_3$ , and  $\text{NaBr}$ . The results are presented as the RU of each tracer. The concentrations of these agents that reduce the RU of the tracer used to half of its maximal value (*i.e.*  $\text{IC}_{50}$ ) are reported in Table 1. For each drug used, the  $\text{IC}_{50}$  was roughly the same for the three tracers for each cell line. Although the values for  $\text{SCN}^-$  and  $\text{I}^-$  are close, it is remarkable how well these selectivities (*i.e.*  $\text{ClO}_4^- > \text{ReO}_4^- > \text{I}^- \geq \text{SCN}^- > \text{ClO}_3^- > \text{Br}^-$ ) agree with previously derived values in thyroid slices for all three tracer anions. The differences between the cell lines are minor for  $\text{NaClO}_4$ ,  $\text{NaSCN}$ , and  $\text{NaReO}_4$  but are higher for NaI, NaBr, and  $\text{NaClO}_3$ , the FRTL5 showing higher  $\text{IC}_{50}$  values than the COS NIS-6 cells. On the other hand, the  $\text{IC}_{50}$  values of any one inhibitory anion within either cell line are consistent against all three tracers, as would be expected. Computer simulations suggest that this discrepancy between cells cannot be accounted for by the presence in FRTL5 cells, but not in the COS NIS-6 cells, of anion channels selective for iodide, bromide, and chlorate. Indeed, under the assumption that the anion flux through the channels is linearly dependent on the intracellular anion concentration (unsaturable process hypothesis in the range of used concentrations), the intracellular amount of radiolabeled anion at steady state is inversely proportional to the first-order kinetic parameter characterizing this flux. Therefore, the ratio of two steady-state amounts of radiolabeled anion obtained with two different concentrations of unlabeled anion is not dependent on this parameter. Thus, the  $\text{IC}_{50}$  is not dependent on the kinetic characteristic of the channel or the amount of the channel present in the cell. On the other hand, species difference of the NIS might conceivably account for it: the NIS expressed in COS NIS-6 cells is human, and, of course, FRTL5 cells express rat NIS. Whatever the explanation, it is clear that NIS exhibits the same selectivity rules that have been established for thyroid tissue long ago.

Dysidenin, a hexachlorinated tripeidelike molecule extracted from the sponge *Dysidea herbacea*, which has lethal effects on fishes and some marine organisms, has been shown to be a strong inhibitor of iodide transport in dog thyroid slices (21). To check whether the transfected NIS exhibited the same property, we studied the effect of dysidenin on the COS NIS-6 cells in comparison with the FRTL5 thyroid cells. In the presence of 20  $\mu\text{M}$  dysidenin, added at the same time as the tracer, the uptake of iodide was rapidly and strongly inhibited in COS NIS-6 cells and in FRTL5 thyroid cells as previously observed in dog thyroid slices. This was also the case for  $^{186}\text{Re}$  perrhenate and  $^{99\text{m}}\text{Tc}$  pertechnetate uptake (data not shown). In experiments performed in both cell lines on the same day and using the same solutions, the residual RU in the presence of dysidenin, at each time of the kinetics (5 min, 15 min, 30 min, 1 h, 2 h) was always lower in FRTL5 cells. A representative experiment performed with radioiodide is presented in Fig. 2. Concentration effect relations were the same in COS NIS-6 and FRTL5 (not shown) and corresponded to those obtained previously in dog thyroid slices (21).

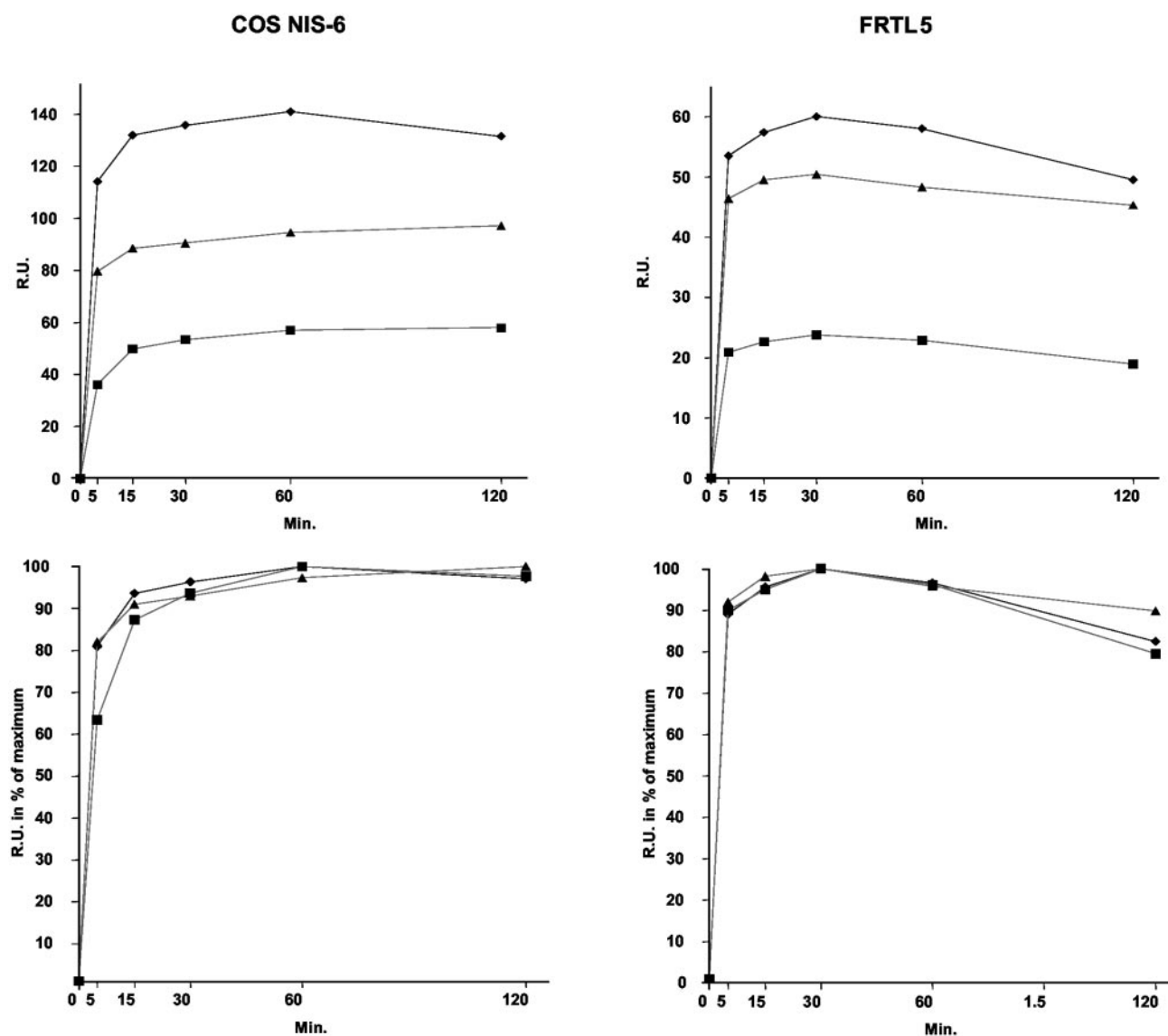


FIG. 1. Kinetics of  $^{125}\text{I}^-$ ,  $^{99\text{m}}\text{TcO}_4^-$ , and  $^{186}\text{ReO}_4^-$  uptake in FRTL5 and COS NIS-6 cells. The experiment was performed according to the protocol outlined in *Materials and Methods*. This is one representative experiment of three for  $^{125}\text{I}^-$  and  $^{99\text{m}}\text{TcO}_4^-$  and two for  $^{186}\text{ReO}_4^-$ . The samples are duplicates in very close agreement.  $^{125}\text{I}$ , ■;  $^{99\text{m}}\text{Tc}$ , ▲;  $^{186}\text{Re}$ , ◆.

### Discussion

The transport properties of the newly cloned  $\text{Na}^+/\text{I}^-$  symporter NIS, as measured by an electrophysiological method based on a stoichiometry of  $2\text{Na}^+$  for  $1\text{I}^-$ , do not completely reproduce the previously established properties of the thyroid cell iodide-trapping system. In particular, NIS in oocytes did not seem to transport the oxyanions perchlorate and perrhenate, whereas thyroid cells do. Such findings run counter to the *in vitro* and *in vivo* data on thyroid slices and whole thyroids. Also, they are not consistent with imaging data with  $^{99\text{m}}\text{Tc}$  pertechnetate or  $^{186}\text{Re}$  perrhenate in the thyroid and stomach (16, 22). Because of the apparent contradiction with electrophysiological findings, we compared  $^{125}\text{I}^-$ ,  $^{99\text{m}}\text{Tc}$  pertechnetate, and  $^{186}\text{Re}$  perrhenate uptake in FRTL5 cells, which exhibit similar transport properties as thyroid cells in slices or primary cultures, with COS-7 cells stably expressing a high density of NIS (COS NIS-6 cells).

FRTL5 and COS NIS-6 cells accumulate the three ions, pertechnetate, perrhenate, and iodide, with the same kinetics in each cell type. The order of uptake for the two cell types is: perrhenate > pertechnetate > iodide, perrhenate, and pertechnetate, often being closer to each other than to iodide. The kinetics of uptake of the three anions and attainment of the steady state is slightly faster for FRTL5 cells than COS NIS-6 cells, which may reflect the existence in FRTL5 cells of exit channels such as those present at the apex of thyroid follicular cells. The faster release of the tracers from FRTL5 cells confirms this conclusion.

The inhibition of the transport of the three radioisotopes by competing anions was then tested. In both types of cells and for each radioisotope, the order of inhibitory potency, presumably reflecting the affinity of the transporter, was  $\text{ClO}_4^- > \text{ReO}_4^- > \text{I}^- \geq \text{SCN}^- > \text{ClO}_3^- \gg \text{Br}^-$ . A summary of these data is presented in Fig. 3. Moreover, dysidenin

TABLE 1. IC<sub>50</sub> of known competing anions of iodide transport, on RU of <sup>125</sup>I<sup>−</sup>, <sup>99m</sup>TcO<sub>4</sub><sup>−</sup>, and <sup>186</sup>ReO<sub>4</sub><sup>−</sup> in COS NIS-6 and FRTL5 cells

Isotope	NaI			NaClO <sub>4</sub>			NaSCN			NaBr			NaClO <sub>3</sub>			NaReO <sub>4</sub>		
	COS NIS-6	FRTL5		COS NIS-6	FRTL5		COS NIS-6	FRTL5		COS NIS-6	FRTL5		COS NIS-6	FRTL5		COS NIS-6	FRTL5	
<sup>125</sup> I <sup>−</sup>	10.3 ± 2.1	51.1 ± 7		0.43 ± 0.1	0.62 ± 0.2		23.5 ± 3	33.6 ± 2		5.944 ± 300	26.250 ± 1.251		131 ± 2	1,368 ± 320		1.12 ± 0.1	1.22 ± 0.05	
<sup>99m</sup> TcO <sub>4</sub> <sup>−</sup>	10.6 ± 1.1	36.9 ± 1.51		0.50 ± 0.035	0.65 ± 0.02		26.8 ± 1.7	32.4 ± 1.5		7,780 ± 1,700	23,271 ± 3,500		130 ± 25	750 ± 110		1.17 ± 0.02	1.96 ± 0	
<sup>186</sup> ReO <sub>4</sub> <sup>−</sup>	9.4 ± 1.4	39.0 ± 4.7		0.41 ± 0.032	0.63 ± 0.03		27.0 ± 1.5	31.2 ± 2.5		7,081 ± 163	30,231 ± 1,391		nd	nd		nd	nd	

The results are expressed in micromolar concentration (μM) ± SD. nd, Not done. The values presented are means of three to eight values depending on the tracer and the agent tested. The RU was measured at 60 min.

inhibits radioiodide transport similarly in both cell types. There is therefore no qualitative difference in the transport of the various tested anions in the thyroid FRTL5 cells and COS NIS-6 cells and thyroid slices, *i.e.* in thyroid cells conserving most of their *in vivo* properties. The apparent discrepancies between NIS and thyroid iodide transport appear not to exist. A thorough discussion of the chemistry underlying this anion selectivity of the iodide-trapping mechanism has been presented previously (6).

What then is the reason for the discrepancy between the electrophysiological and the tracer uptake experiments? Although Eskandari *et al.* (9) stated, “Our data cannot exclude electroneutral Na<sup>+</sup>/ClO<sub>4</sub><sup>−</sup> transport,” the same group later went further and proposed that the “NIS inhibitor, perchlorate, is not translocated by NIS into the cell” (23). The same argument applies to perrhenate, which, according to the electrophysiological measurement, was also not transported by NIS and presumably to pertechnetate, although the latter anion was not tested by these authors. The data on perrhenate and pertechnetate presented here clearly demonstrate that NIS mediates such transport. A possible explanation of the discrepancy might be that, at the high anion concentration required for the electrophysiological measurements (500 μM), another less specific transporter or channel becomes activated and could have masked the effect of NIS. This is especially pertinent for the oxyanions whose Km or Ki values are substantially lower than those for iodide (1). Indeed the use of such high concentrations might explain another discrepancy: although ClO<sub>3</sub><sup>−</sup> has a very low affinity as an inhibitor of NIS, it was ranked first after iodide and before SCN<sup>−</sup> in the electrophysiological measurements. This poor potency contradicts the statement, “given that chlorate is readily translocated via NIS into the cell” (23), and rules out the hypothesis that ClO<sub>3</sub><sup>−</sup> uptake might have accounted for the previously observed uptake of ClO<sub>4</sub><sup>−</sup> in thyroid cells (13, 14). Although direct perchlorate uptake has not been demonstrated, for lack of commercially available isotope, the evidence that it behaves as its chemical analog perrhenate and pertechnetate is overwhelming. The great chemical similarity among the tetrahedral oxyanions, and the even greater biological similarity detailed in virtually all published work, suggests that perchlorate is handled by NIS and the thyroid as are perrhenate and pertechnetate. In addition, all direct transport experiments on the accumulation of labeled perchlorate by the thyroid (19), and especially the work of Chow *et al.* (13), provide convincing evidence that perchlorate can be transported by the NIS mechanism.

The most likely explanation for the discrepancy between electrophysiological and tracer uptake measurements of tetrahedral oxyanion transport would be that the symporter would have equal stoichiometry for Na<sup>+</sup> and these anions, *i.e.* that this transport would be electrically neutral. The 2/1 stoichiometry has also been questioned for SCN<sup>−</sup> by Yoshida *et al.* (10), who suggested a higher value for this ratio.

We conclude then that NIS clearly mediates the transport of ReO<sub>4</sub><sup>−</sup>, TcO<sub>4</sub><sup>−</sup>, and by inference ClO<sub>4</sub><sup>−</sup>, but the mechanism by which this occurs, whether electrically neutral cotransport with sodium ion or by an alternative energy source, remains to be determined.

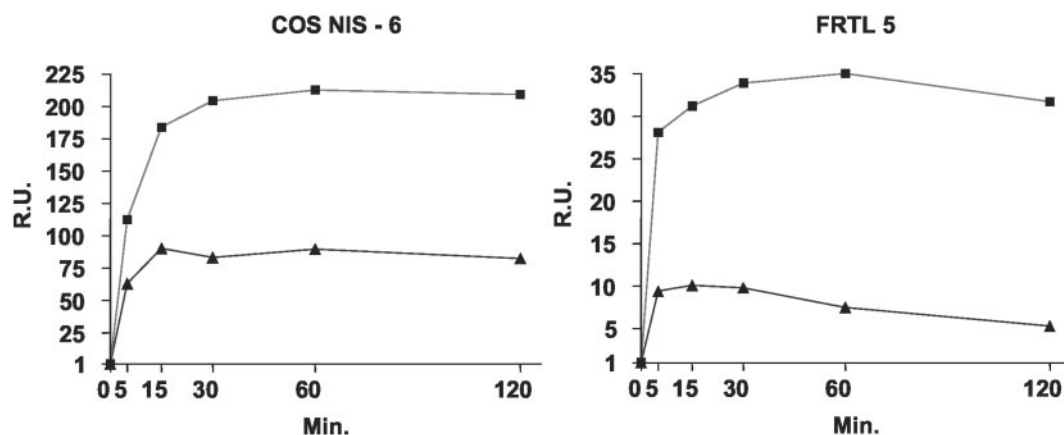


FIG. 2. Effect of dysidenin on RU of  $^{125}\text{I}^-$  in COS NIS-6 and FRTL5 cells. Dysidenin was added at the same time as the tracer. Control, ■; dysidenin 20  $\mu\text{M}$ , ▲.

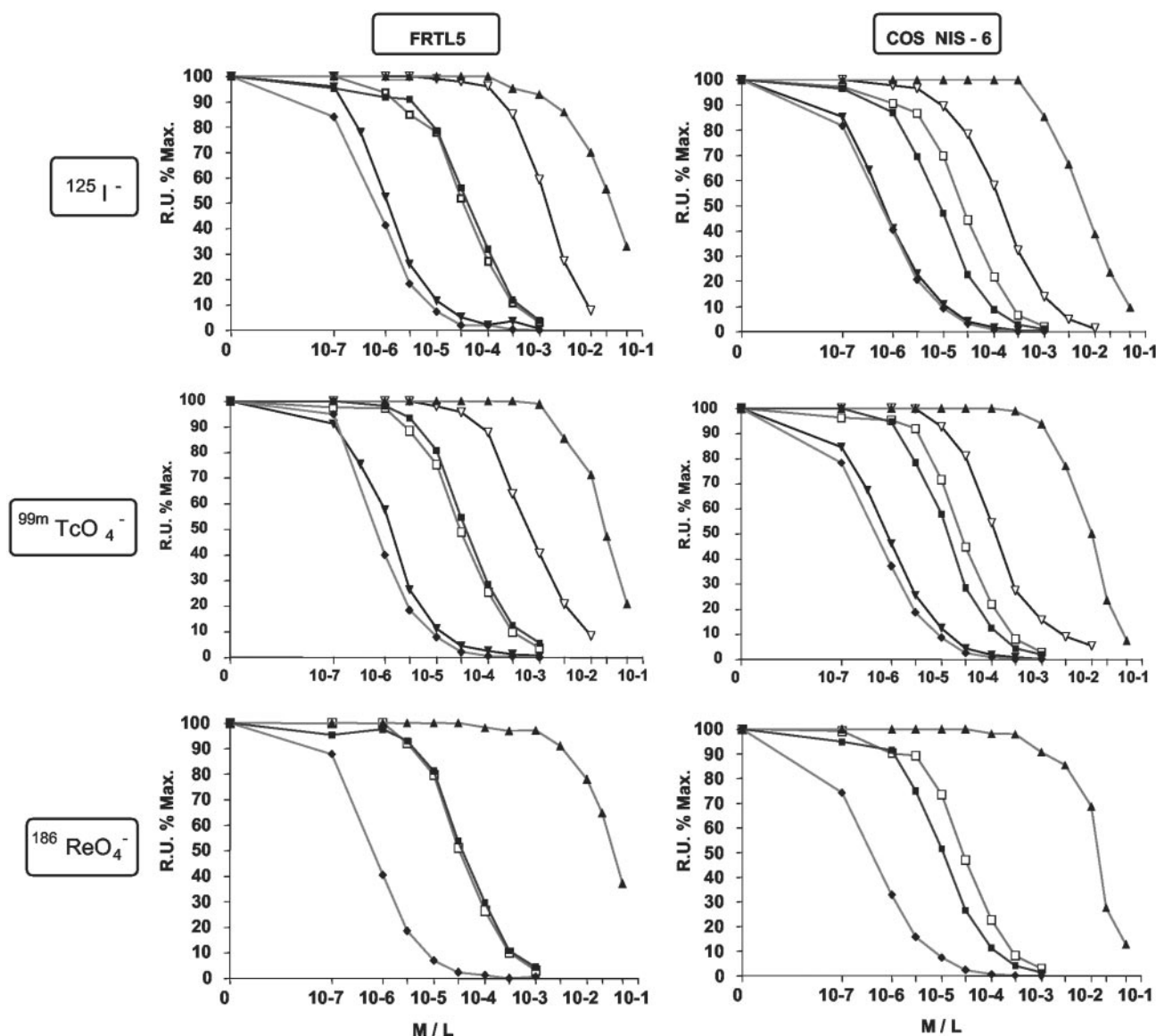


FIG. 3. Inhibition of the transport of  $^{125}\text{I}^-$ ,  $^{99\text{m}}\text{TcO}_4^-$ , and  $^{186}\text{ReO}_4^-$  by competing anions in FRTL5 and COS NIS-6 cells. The competitor and tracer anions were added together, and the uptake was measured after 1 h. NaI, ■; NaBr, ▲;  $\text{NaClO}_4$ , ◆;  $\text{NaClO}_3$ , ▽; NaSCN, □;  $\text{NaReO}_4$ , ▼.

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## References

- Wolff J 1964 Transport of iodide and other anions in the thyroid gland. *Physiol Rev* 44:45–90
- Carrasco N 1993 Iodide transport in the thyroid gland. *Biochim Biophys Acta* 1154:65–82
- Iff HW, Wilbrandt W 1963 The dependence of iodine accumulation in thyroid slices on the ionic composition of the incubation medium: influence of cardiac glycosides. *Biochim Biophys Acta* 70:711–752
- Bagchi N, Fawcett DM 1973 Role of sodium ion in active transport of iodide by cultured thyroid cells. *Biochim Biophys Acta* 318:235–251
- Tyler DD, Gonze J, Lamy F, Dumont JE 1968 Influence of mitochondrial inhibitors on the respiration and energy-dependent uptake of iodide by thyroid slices. *Biochem J* 106:123–133
- Wolff J 1983 Congenital goiter with defective iodide transport. *Endocr Rev* 4:240–254
- Dai G, Levy O, Carrasco N 1996 Cloning and characterization of the thyroid iodide transporter. *Nature* 379:458–460
- Levy O, Ginter CS, De la Vieja A, Levy D, Carrasco N 1998 Identification of a structural requirement for thyroid  $\text{Na}^+/\text{I}^-$  symporter (NIS) function from analysis of a mutation that causes human congenital hypothyroidism. *FEBS Lett* 429:36–40
- Eskandari S, Loo DD, Dai G, Levy O, Wright EM, Carrasco N 1997 Thyroid  $\text{Na}^+/\text{I}^-$  symporter. Mechanism, stoichiometry, and specificity. *J Biol Chem* 272:27230–27238
- Yoshida A, Sasaki N, Mori A, Taniguchi S, Mitani Y, Ueta Y, Hattori K, Sato R, Hisatome I, Mori T, Shigemasa C, Kosugi S 1997 Different electrophysiological character of  $\text{I}^-$ ,  $\text{ClO}_4^-$ , and  $\text{SCN}^-$  in the transport by  $\text{Na}^+/\text{I}^-$  symporter. *Biochem Biophys Res Commun* 231:731–734
- Yoshida A, Sasaki N, Mori A, Taniguchi S, Ueta Y, Hattori K, Tanaka Y, Igawa O, Tsuboi M, Sugawa H, Sato R, Hisatome I, Shigemasa C, Grollman EF, Kosugi S 1998 Differences in the electrophysiological response to  $\text{I}^-$  and the inhibitory anions  $\text{SCN}^-$  and  $\text{ClO}_4^-$ , studied in FRTL-5 cells. *Biochim Biophys Acta* 1414:231–237
- Anbar M, Guttmann S, Lewitus Z 1959 The mode of action of perchlorate ions on the iodine uptake of the thyroid gland. *Int J Appl Radiat Isotopes* 7:87–96
- Chow SY, Chang LR, Yen MS 1969 A comparison between the uptakes of radioactive perchlorate and iodide by rat and guinea-pig thyroid glands. *J Endocrinol* 45:1–8
- Chow SY, Woodbury DM 1970 Kinetics of distribution of radioactive perchlorate in rat and guinea-pig thyroid glands. *J Endocrinol* 47:207–218
- Wolff J 1998 Perchlorate and the thyroid gland. *Pharmacol Rev* 50:89–105
- Lin WY, Hsieh JF, Tsai SC, Yen TC, Wang SJ, Knapp Jr FF 2000 A comprehensive study on the blockage of thyroid and gastric uptakes of  $^{188}\text{Re}$ -perrhenate in endovascular irradiation using liquid-filled balloon to prevent restenosis. *Nucl Med Biol* 27:83–87
- Dadachova E, Bouzahzah B, Zuckier LS, Pestell RG 2002 Rhenium-188 as an alternative to iodine-131 for treatment of breast tumors expressing the sodium/iodide symporter (NIS). *Nucl Med Biol* 29:13–18
- Wolff J, Maurey JR 1963 Thyroidal iodide transport. IV. The role of ion size. *Biochim Biophys Acta* 69:58–67
- Wolff J 2002 A miss for NIS? *Thyroid* 12:295–297
- Pohlentz J, Duprez L, Weiss RE, Vassart G, Refetoff S, Costagliola S 2000 Failure of membrane targeting causes the functional defect of two mutant sodium iodide symporters. *J Clin Endocrinol Metab* 85:2366–2369
- Van Sande J, Deneubourg F, Beauwens R, Braekman JC, Daloze D, Dumont JE 1990 Inhibition of iodide transport in thyroid cells by dysidenin, a marine toxin, and some of its analogs. *Mol Pharmacol* 37:583–589
- Kotzerke J, Fenchel S, Guhlmann A, Stabin M, Rentschler M, Knapp Jr FF, Reske SN 1998 Pharmacokinetics of  $^{99}\text{TcO}_4^-$ -pertechnetate and  $^{188}\text{ReO}_4^-$ -perrhenate after oral administration of perchlorate: option for subsequent care after the use of liquid  $^{188}\text{ReO}_4^-$  in a balloon catheter. *Nucl Med Commun* 19:795–801
- De La Vieja A, Dohan O, Levy O, Carrasco N 2000 Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. *Physiol Rev* 80:1083–1105