BASIC SCIENCE INVESTIGATIONS

Stunning of Iodide Transport by ^{131}I Irradiation in Cultured Thyroid Epithelial Cells

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The existence of thyroid stunning (i.e., inhibited thyroidal iodide uptake after administration of diagnostic amounts of ^{131}I) is controversial and is currently a subject of debate. To our knowledge, the stunning phenomenon has not been investigated previously in vitro. **Methods:** Growth-arrested porcine thyroid cells that formed a tight and polarized monolayer in a bicameral chamber were irradiated with 3–80 Gy ^{131}I present in the surrounding culture medium for 48 h. The iodide transport capacity after irradiation was evaluated 3 d later by measuring the transepithelial (basal to apical) flux of trace amounts of ^{125}I. **Results:** The basal-to-apical ^{125}I transport decreased with increasing absorbed dose acquired from ^{131}I; a nearly 50% reduction was observed already at 3 Gy. Stable iodide at the same molarity as ^{131}I (10^{-8} mol/L) had no effect on the ^{125}I transport. Cell number and epithelial integrity were not affected by irradiation. **Conclusion:** Stunning of iodide transport is detected after ^{131}I irradiation of cultured thyroid cells. The degree of inhibition of transport is dependent on the absorbed dose.

Key Words: radioiodide; stunning; thyroid; ^{131}I

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As stated in a recent review, "Evidence that stunning is a real phenomenon is now strong, albeit not yet conclusive" (*1*). This quotation summarizes the current view on the potential side effects of diagnostic amounts of ^{131}I on subsequent radiation therapy due to inhibited iodide accumulation in thyroid tissue. Radioiodide has been used in therapy for >50 y. Thyroid stunning was first reported in 1951 by Rawson et al. (*2*), who found that the ^{131}I uptake, as determined by scintigraphy, was reduced after administration of diagnostic amounts of ^{131}I. However, the question of whether preexposure to diagnostic amounts of ^{131}I might influence the outcome of ^{131}I radiation therapy is still being debated (*3–10*).

Efforts to identify and determine the magnitude of thyroid stunning in response to ^{131}I radiation are based solely on in vivo studies. A measured reduction in thyroid uptake might be caused by stunning or dead-time losses related to high counting rates if not compensated for. McDougall (*8*) concluded that no stunning was observed in his study when the administered activity was <74 MBq ^{131}I. However, other studies reported stunning when activities of >111 MBq were used (*9,10*). The use of ^{123}I for diagnostics to eliminate the stunning effect has been recommended in some reports (*11–13*).

The mechanism by which thyroid stunning, if existing, occurs is unknown. Leger et al. (*9*), who described a 50% decrease in the uptake of ^{123}I 5 wk after administration of 185 MBq ^{131}I, suggested 2 possible mechanisms. One is simply that the β-emission of ^{131}I given for diagnostic purposes is enough to cause cell damage, perhaps by induction of apoptosis, thereby reducing the number of iodide-transporting cells. The alternative explanation is that low-dose ^{131}I radiation in some way affects iodide transport mechanisms, possibly also involving a change in the intrathyroidal iodide turnover, without being deleterious to cell viability.

This study was performed to determine if absorbed doses of ^{131}I that are comparable with those used in clinical diagnostic investigations with ^{131}I could induce stunning of iodide transport in thyroid cells in vitro. For this purpose, we used a bicameral culture system that mimics the structural and functional properties of the follicular epithelium in intact thyroid tissue.

MATERIALS AND METHODS

Cell Culture

Porcine thyroids obtained from the local abattoir were prepared according to Nilsson et al. (*14*) to obtain a pure fraction of follicular cells. Briefly, glands sterilized by flaming for 5 s in 70%

ethanol were decapsulated and freed from macroscopic connective tissue, after which the parenchyme was subjected to enzymatic disintegration by collagenase. Segments of thyroid follicles were separated from large tissue fragments and blood cells by repeated centrifugation and filtration and then suspended in minimal essential medium supplemented with 5% fetal calf serum, penicillin (200 U/mL), streptomycin (200 μg/mL), and fungizone (2.5 μg/mL) (all culture medium constituents were purchased from GIBCO, Paisley, U.K.). The cells were cultured on the collagen-coated microporous filters (pore size, 0.4 μm) of bicameral chambers (Transwell 3413; Corning Costar, Cambridge, MA) at 37°C in an incubator with 5% CO_2; the culture medium was exchanged every 2–3 d. During culture the growing cells reorganized spontaneously from follicular aggregates to form a continuous monolayer on the filter. Thus, the experimental system provides a model consisting of 3 compartments (Fig. 1) corresponding to the in vivo counterparts: the follicular epithelium (cell monolayer), the extrafollicular space (basal volume), and the follicular lumen (apical volume).

To evaluate the barrier function of the cell layer before and during experiments, the transepithelial resistance was measured with a Millicell ERS ohmmeter (Millipore Corp., Bedford, MA). As described earlier (15), the monolayered cells we used for the radioiodide experiments were largely nondividing because of contact-dependent inhibition of growth. Cell number was estimated by determination of the total DNA content (16).

Irradiation Procedures

In the standard experimental protocol (Fig. 2), cultures were pretreated with 1 mU/mL thyroid-stimulating hormone ([TSH]
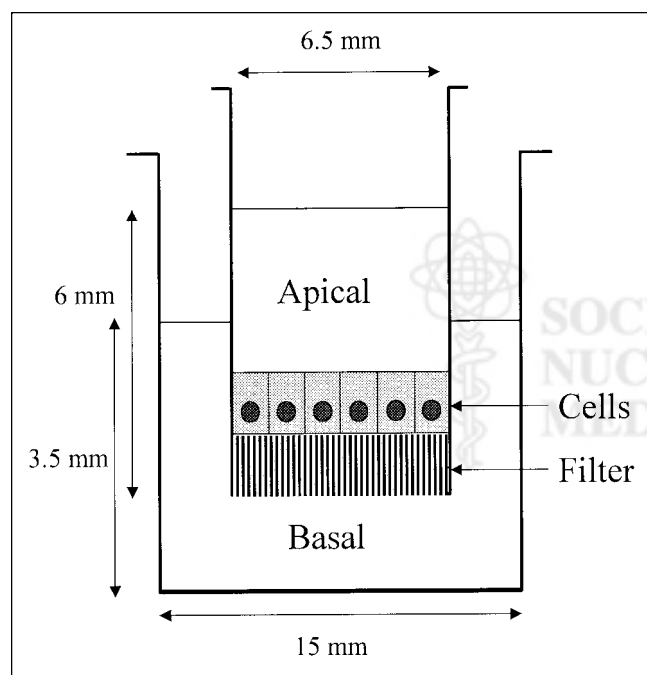

FIGURE 1. Transwell bicameral culture chamber system. Porcine thyroid cells form continuous monolayer epithelium on microporous filter, which constitutes bottom of Transwell insert. Monolayer is continuous and thus separates chamber into lower (basal) and upper (apical) compartment. Insert that holds filter is placed at fixed distance of 1 mm from base of basal well. Filter area, 0.33 cm²; filter height, 10 μm; filter pore size, 0.4 μm.

Sigma Chemical Co., St. Louis, MO) for 48 h before irradiation to accelerate the iodide transport capacity. TSH stimulation was also maintained throughout irradiation and subsequent steps of the experiment. Irradiation was started by replacing the culture medium with medium containing ^{131}I (Nycomed Amersham Plc., Little Chalfont, U.K.) and, to prevent radioiodide-protein binding and possible confounding side effects of iodinated compounds, 1 mmol/L methimazole (Sigma) was added. The addition of alkaline ^{131}I stock solution, finally diluted 1:500 or more, to minimal essential medium did not change the pH. The medium with radioactivity was distributed, 500 μL in the basal compartment and 100 μL in the apical compartment. The activity concentration was the same basally and apically at the start of incubation. Assuming that the ratio of apical and basal radioactivity concentrations did not change over time, different amounts of ^{131}I estimated to give absorbed doses of 1, 5, 10, and 30 Gy were added to the cultures. To more accurately determine the actual absorbed dose, taking into account changes in the distribution of radioactivity likely to occur because of ongoing transport, the ^{131}I activity was determined in consecutive samples of the basal and apical media during irradiation. In such experiments, the starting volumes were 400 and 200 μL and the sampling volumes were 10 and 5 μL, respectively, to maintain a constant volume ratio between the compartments on either side of the cell monolayer. In some experiments, 1 mmol/L perchlorate (Sigma) was present in the culture medium throughout irradiation to block the accumulation of ^{131}I in the apical compartment. To investigate the possible effects of iodide per se on ^{125}I transport, irradiated cultures were compared with those that were exposed to stable iodide, ^{127}I, at similar molarity (10^{-8} mol/L). Untreated control cultures were included in all experiments. In general, each type of experiment was repeated 3 times on cultures from different platings. The 48-h irradiation period was terminated by multiple, gentle washings in culture medium to remove all radioactivity, after which the culture was continued until transport studies were performed.

Measurement of Iodide Transport

The ability of the cells to transport iodide was evaluated 3 d after terminating the irradiation period. The chambers were transferred from the incubator to a 37°C water bath, and the culture medium was replaced by Tyrode's salt solution, pH 7.2, containing 1 mmol/L methimazole to prevent iodination. To study the transport of iodide in the basal-to-apical direction, ^{125}I (Nycomed Amersham) was added to the basal medium (150 kBq/mL; 400 μL) and the radioactivity accumulated in the apical medium (200 μL) was analyzed in 150-μL samples. The samples were taken at 10-min intervals for 30 min, and the collected volume was replaced immediately with nonradioactive medium. The remaining 50 μL of apical medium at each interval was left in to minimize the risk of damaging the cell layer with the tip of the pipette. Finally, the filters and cells were washed twice and cut out of the holders. The ^{125}I activities present in the apical medium, the basal medium, and the filters with adherent cells were measured using a Wallac 1480 γ-counter (Wallac Oy, Turku, Finland). Corrections were made for background, radioactive decay, and, when appropriate, spillover in the ^{125}I energy window from photons emitted by the minimal amounts of ^{131}I remaining in filters and cells after the wash.

Absorbed Dose Calculations

The absorbed dose of ^{131}I applied to the cells was initially estimated by assuming that the activity was distributed evenly
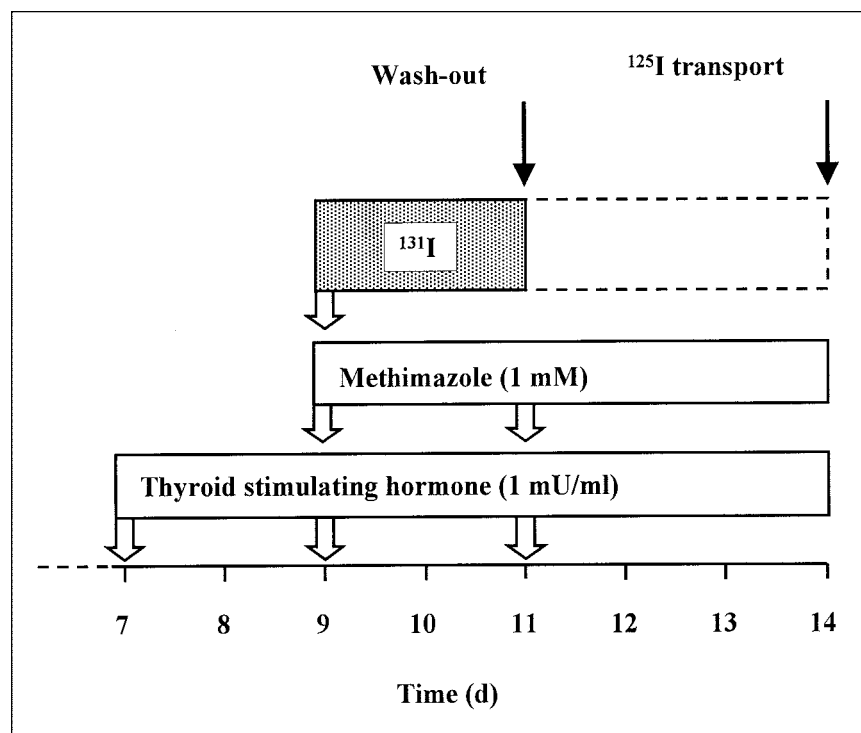
FIGURE 2. Protocol for thyroid cell culture treatments (open arrows) and radioiodide transport analysis (filled arrows). Time scale indicates number of days after starting primary culture.

between the culture chamber compartments. The distance from the cell layer to the wall of the chamber and medium surfaces was greater than the continuous slowing-down approximation range of the emitted particles. Therefore, the absorbed dose affecting the cells was assumed to be close to the average absorbed dose in the chamber and was calculated according to:

$$\bar{D} = \frac{\tilde{A} \cdot \Delta \cdot \phi}{m},$$

where $\tilde{A}$ is the cumulated activity, Δ is the energy emitted per transition, ϕ is the absorbed fraction, and m is the mass of cells (17). The absorbed fraction was set to 1 for electrons and calculated to be 0.0125 for photons (364 keV), using the method from the International Commission on Radiation Units and Measurements (17):

$$\phi(x) = 0.75(1 - e^{\mu_{en} \cdot x}),$$

where μ_{en} is the mass energy–absorption coefficient and x is the radius of the compartment. This approximation can be used assuming that the product of $\mu_{en}x \ll 1$, the volume is approximated by a sphere, and the radioactivity is distributed homogeneously within the volume. However, during the time course of irradiation a net transport of ^{131}I through the cell layer occurred in the apical direction, resulting in a gradual change in the apical-to-basal radioiodide concentration ratio (Fig. 3). In most experiments, the concentration of ^{131}I in the apical medium was 100–300 times higher than that in the basal medium when irradiation was stopped after 48 h. Taking into account the different ^{131}I concentrations and geometries of the apical and basal compartments, the corrected absorbed dose, D_c, was calculated according to:

$$D_c = D_0 \frac{(1 + C_{AB})(V_A + V_B)}{2(V_A \cdot C_{AB} + V_B)},$$

where D_0 is the uncorrected absorbed dose as determined by the equations above, C_{AB} is the apical-to-basal ^{131}I concentration ratio, and V_A and V_B are the apical and basal volumes, respectively (Fig. 1). Theoretically, if the entire radioactivity were transferred instantly to the apical compartment, the absorbed dose would be 3 times higher than if the applied radioactivity were to remain at a ratio of 1:1 between the 2 compartments. On the basis of the kinetics of the gradual accumulation of ^{131}I in the apical medium, as illustrated in Figure 3, the absorbed doses were adjusted by introducing an average correction factor of 2.7.

Statistical Analysis

The Student t test was used to determine the statistical significance of differences between the groups. Results are given as mean ± SEM.

RESULTS

The ability of the cells to unidirectionally transfer ^{125}I from the basal to the apical medium, corresponding to the natural route of transepithelial iodide transport in vivo, was studied 3 d after terminating the ^{131}I irradiation. Before each transport experiment, the tightness of the cell layer was confirmed by measurements of the transepithelial electrical resistance. No signs of paracellular leakage were found, regardless of whether the cells had been exposed to ^{131}I. ^{125}I transport was almost completely blocked in cultures irradiated with 80 Gy (Fig. 4). In contrast, no significant change in the ^{125}I transport capacity of the cells was found in the presence of 10^{-8} mol/L stable iodide (Fig. 4), which is equivalent to the highest ^{131}I molarity used. Lower absorbed doses also reduced the basal-to-apical transport of ^{125}I (Fig. 5). The ^{125}I transport was decreased by nearly 50% already
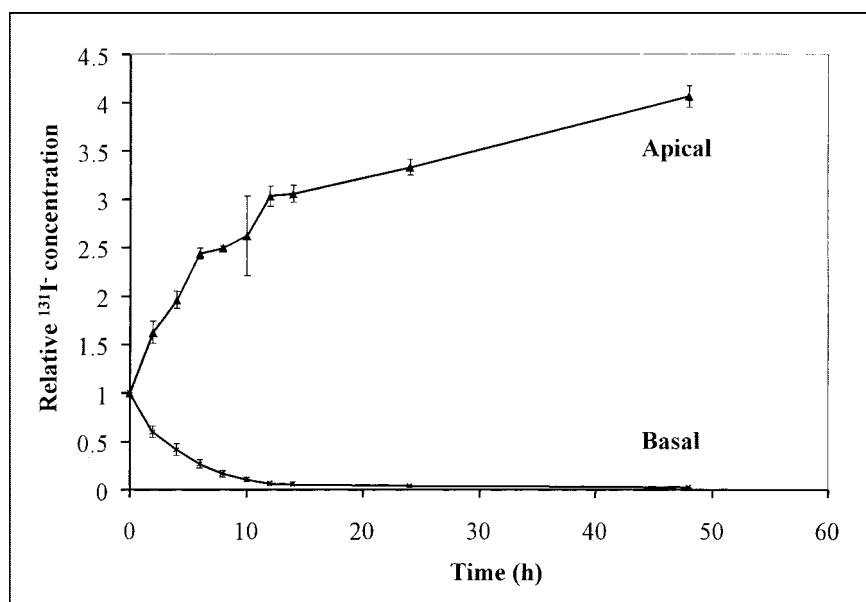
FIGURE 3. Redistribution of ^{131}I between basal and apical media of filter-cultured porcine thyrocytes during irradiation period ($D_c = 15$ Gy). Equal concentrations of ^{131}I were present initially at both sides of cell monolayer. Results are presented as mean ± SEM ($n = 6$).

at 3 Gy compared with the control group. Perchlorate present during irradiation to prevent accumulation of ^{131}I in the apical medium partially blocked the reduction of ^{125}I transport appearing at the corresponding absorbed dose (Fig. 6). Determination of the DNA content revealed that ^{131}I radiation at doses that caused pronounced inhibition of the ^{125}I transport did not change significantly the total number of cells (Table 1).

DISCUSSION

In this study, we examined whether ^{131}I at absorbed doses commonly obtained from diagnostic investigations are able to induce stunning of thyroid iodide transport in vitro.

Porcine thyroid cells were cultured in Transwell bicameral chambers to provide an experimental system in which parameters affecting the viability and function of the cells as a polarized epithelium could be controlled and monitored (14). The cells were prestimulated with TSH to maintain the iodide-transporting capacity close to its maximal level (14) and then irradiated with ^{131}I for 2 d. To rule out side effects related to iodination, such as reduced expression of the sodium/iodide symporter (18), the thyroid-blocking agent methimazole was present throughout ^{131}I exposure. Iodide transport was evaluated 3 d after washing out the radioactivity by measurements of the transepithelial transport of trace amounts of [125]I. Clinical studies have not elucidated
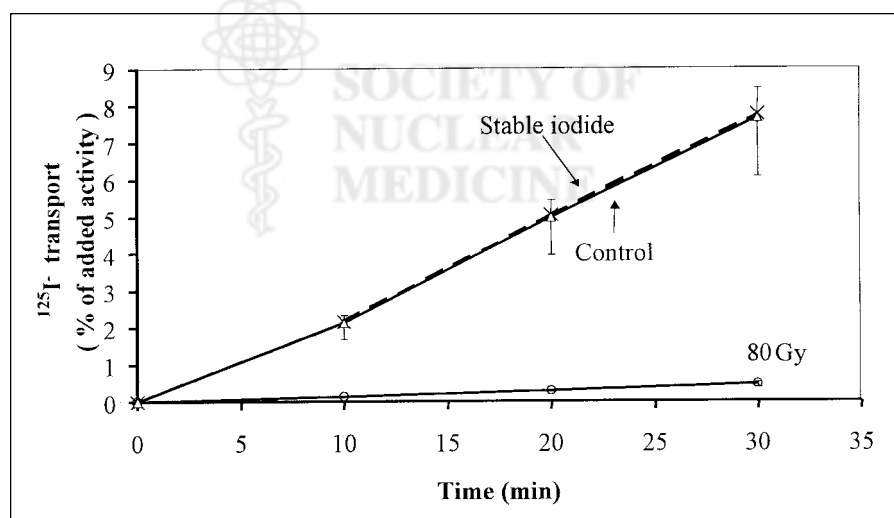

FIGURE 4. Effect of ^{131}I irradiation ($D_c = 80$ Gy) and equimolar concentrations of stable iodide (10^{-8} mol/L) on subsequent (3 d later) basal-to-apical ^{125}I transport. Results are given as ^{125}I activity transported into apical medium at indicated times relative to activity added to basal medium at time = 0. Values obtained are expressed as percentage of total activity present basally at start of experiment. Results are expressed as mean ± SEM ($n = 3$).
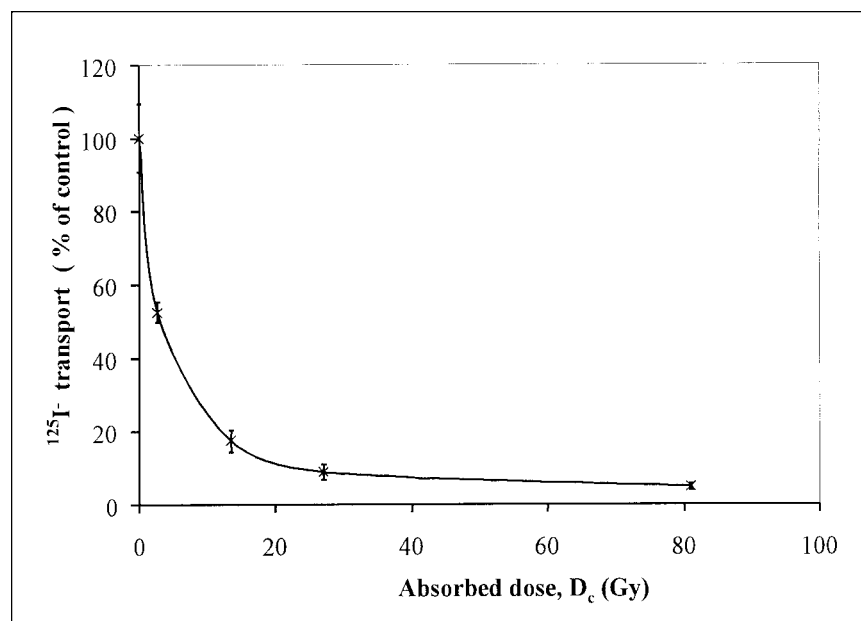
FIGURE 5. Effect of different absorbed doses on iodide transport in ^{131}I irradiated cultures. Results are presented as relative amount of ^{125}I activity transported from basal to apical medium during 30 min. Values are given as mean ± SEM ($n = 4$).

whether the reduction in radioiodide uptake observed after administration of diagnostic amounts of ^{131}I is caused by a decrease in activity of the iodide-concentrating mechanism or merely reflects a therapeutic effect related to radiation-induced cell death. Our results show that ^{131}I radiation for 48 h reduces the vectorial (basal to apical) [125]I transport across filter-cultured porcine thyrocytes in a dose-dependent way. A 50% inhibition of transport was noted at an absorbed dose of approximately 3 Gy (Fig. 5). The lack of effect of stable iodide present for the same period of time at a concentration (10^{-8} mol/L) similar to that of the highest ^{131}I concentration proves that the stunning effect is radiation dependent and is not related to iodide exposure per se (Fig. 4). This notion is supported further by the results of the perchlorate experiment (Fig. 6). Iodide uptake mediated by the sodium/iodide symporter is known to be blocked by perchlorate (*19*). Perchlorate was found to counteract stun-

ning, and a likely explanation is that a lower absorbed dose was obtained because of the reduced apical ^{131}I accumulation.

To eliminate misleading results due to changes in cell number, this study was designed to examine the effect of ^{131}I on iodide transport in confluent, nondividing cells. On the basis of ^{3}H-thymidine incorporation experiments (data not shown), it is evident that irradiation equivalent to the applied absorbed doses used in this study inhibits the proliferation of subconfluent, rapidly growing thyroid cells. Therefore, irradiation might very well influence cell renewal in the monolayer. However, because this is known to occur at a very low rate in contact-inhibited, high-density cultures, it is likely that any small loss in cell number due to cell cycle arrest contributes only marginally to the pronounced reduction in iodide transport observed 3 d after irradiation was terminated. The similar levels of total DNA
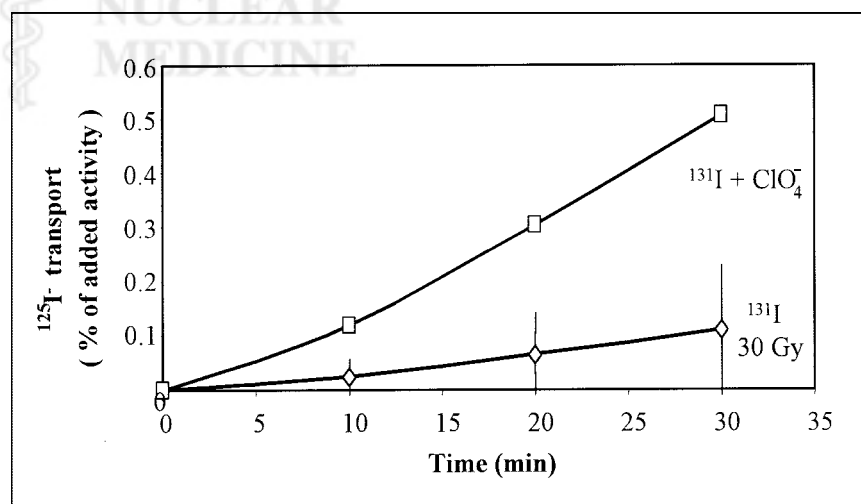

FIGURE 6. Effect of perchlorate (ClO$_4^-$) on iodide transport in ^{131}I-irradiated cultures. Perchlorate (1 mmol/L) was present in apical and basal media during exposure to [131]I (corresponding to $D_c = 30$ Gy without perchlorate) for 48 h. [125]I transport was evaluated 3 d later. ^{131}I-induced stunning of ^{125}I transport was 90% when perchlorate was not present during irradiation. Results are expressed as mean ± SEM ($n = 3$).

TABLE 1
Effect of [131]I Radiation on DNA Content in Confluent, Growth-Arrested Porcine Thyrocytes Cultured on Filter

Experiment*	Radiation†	DNA‡	
		µg/filter	%
1	−	1.48 ± 0.57	100
	+	1.32 ± 0.18	89
2	−	1.42 ± 0.14	100
	+	1.12 ± 0.21	79
3	−	2.26 ± 0.23	100
	+	1.95 ± 0.13	86
4	−	1.13 ± 0.54	100
	+	1.36 ± 0.18	120

*Cells from different platings.

†Irradiation for 48 h, corresponding to corrected absorbed dose of 13.5 Gy.

‡Cells were taken for DNA quantification 3 d after ending ^{131}I radiation. No statistically significant differences were obtained between irradiated and control cultures. Results are presented as mean ± SEM ($n = 3$).

obtained in the irradiated and nonirradiated cultures (Table 1) confirmed this assumption. Cell density, as revealed by light microscopic examination after nuclear staining (data not shown), was also the same with and without pretreatment with [131]I. Preliminary observations on caspase-3 activity and nuclear morphology (data not shown) suggest that apoptosis was not induced by ^{131}I radiation under the current experimental conditions.

The irradiated cells were also evaluated by measuring the transepithelial resistance before the ^{125}I transport was studied. A high resistance indicates that leaky tight junctions or ruptured plasma membranes due to cell damage cannot be present. We found that the barrier function of the cell layer did not change, even after the highest absorbed dose (80 Gy). That the integrity of the cultured epithelium was maintained is supported further by the observation of a high apical-to-basal ^{131}I ratio in the bicameral culture chamber at the end of irradiation. Also, the pronounced reduction in iodide transport observed 3 d later is compatible only with a continuous and tight cell layer attached to the filter. Indeed, an impaired epithelial barrier would result in the unrestricted diffusion of solutes, including iodide, between the basal and apical compartments (i.e., the reverse of the actual findings in the irradiated cultures) (20).

When ^{131}I was added at the start of the experiment, the apical and basal iodide molarities were equal. However, during the course of irradiation the ability of the cells to transport iodide generated a gradual accumulation of the radionuclide in the apical medium, resulting in a very high apical-to-basal ^{131}I ratio after 48 h. The enrichment of most of the ^{131}I in the smaller apical volume requires the absorbed dose, initially calculated on the basis of the assumption of a constant apical-to-basal ratio of 1, to be corrected. The estimated correction factor was approximately 2.7 taking

into account the kinetics of the ^{131}I accumulation in the apical medium (Fig. 3). The maximum error in D_c was estimated to be ±10%. That ^{131}I transport prevailing during irradiation indeed caused an increased absorbed dose to the cells was shown in experiments in which the generation of a high apical-to-basal ^{131}I gradient was inhibited by perchlorate.

The estimated absorbed doses reported to induce thyroid stunning in previous in vivo studies vary. Muratet et al. (21) showed stunning in a group of patients who received an absorbed dose of >17.5 Gy to thyroid remnants after ^{131}I scanning. Kao and Yen (10) observed a 74% reduction in radioiodide uptake when the diagnostic absorbed dose was >35 Gy. Sabri et al. (22) reported stunning at similar absorbed doses. Our findings of inhibited ^{125}I transport by approximately 90% at 30 Gy and almost 50% at 3 Gy (corrected absorbed doses) in the ^{131}I-irradiated thyroid cell cultures suggest that thyroid stunning may occur also at lower absorbed doses than those considered on the basis of clinical observations. Another matter of concern, which has been discussed only briefly in previous in vivo studies, is the time of onset and the duration of thyroid stunning. Indeed, the variation in time between the administration of diagnostic and therapeutic amounts of ^{131}I is considerable. Recently, McDougall (8) and Cholewinski et al. (3) found no signs of inhibited uptake when therapy was performed 72 h or earlier after diagnostic examination using 74 MBq and 185 MBq ^{131}I, respectively. This suggests that stunning might be manifest after a delay of a few days. To reproduce a time interval of relevance in clinical applications, the iodide transport was evaluated 3 d after ending the 48-h irradiation period. The fact that the inhibition of iodide transport in cultured thyrocytes was pronounced only 5 d after the start of irradiation indicates that stunning must be initiated earlier. In future studies, the in vitro model will be useful to determine more precisely the kinetics of radioiodide-induced thyroid stunning and its dependence on the absorbed dose for different iodine isotopes.

CONCLUSION

This study shows that incubation with ^{131}I inhibits the transepithelial transport of ^{125}I in cultured porcine thyroid cells. The reduction in transport is not related to possible side effects of stable iodide or loss of damaged cells but is interpreted as a direct effect of radiation on thyroid function. Thus, the results provide in vitro evidence favoring the hypothesis that thyroid stunning is a real phenomenon that must be considered in radiation therapy.

ACKNOWLEDGMENTS

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