Transcytosis in Thyroid Follicle Cells

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ABSTRACT Inside-out follicles prepared from pig thyroid glands were used for studies on endocytosis. In this in vitro system, only the apical plasma membranes of follicle cells were exposed to tracers added to the culture medium. Cationized ferritin (CF) bound to the apical plasma membrane and was transferred first to endosomes and to lysosomes (within 5 min). Later, after ~30 min, CF was also found in stacked Golgi cisternae. In addition, a small fraction of endocytic vesicles carrying CF particles became inserted into the lateral (at ~11 min) and the basal (at ~16 min) plasma membranes. Morphometric evaluation of CF adhering to the basolateral cell surfaces showed that the vesicular transport across thyroid follicle cells (transcytosis) was temperature-sensitive; it ceased at 15°C but increased about ninefold in follicles stimulated with thyrotropin (TSH).

Thyroglobulin-gold conjugates and [3H]thyroglobulin (synthesized in separate follicle preparations in the presence of [3H]leucine) were absorbed to the apical plasma membrane and detected mainly in lysosomes. A small fraction was also transported to the basolateral cell surfaces where the thyroglobulin preparations detached and accumulated in the newly formed central cavity. As in the case of CF, transcytosis of thyroglobulin depended on the stimulation of follicles with TSH.

The observations showed that a transepithelial vesicular transport operates in thyroid follicle cells. This transport is regulated by TSH and includes the transfer of thyroglobulin from the apical to the basolateral plasma membranes. Transcytosis of thyroglobulin could explain the occurrence of intact thyroglobulin in the circulation of man and several mammalian species.

Thyroglobulin, the macromolecular secretory product of thyroid follicle cells, is released by exocytosis at the apical plasma membrane and stored in the follicle lumen (2, 31; for reviews see 10, 16, 50). There it is enclosed by the follicle cells, which form a tight epithelial monolayer and a barrier against the diffusion of thyroglobulin into the interfollicular space (43). Because of the unique structural and functional organization of the thyroid gland, thyroglobulin was thought to be confined to the follicles. However, intact thyroglobulin has unquestionably been detected outside the follicles (a) in the serum of man and of other mammalian species, with the aid of specific radioimmunoassays (7, 37, 48), and (b) immunocytochemically in the lymphatic vessels of thyroid tissue (3). The concentration of thyroglobulin in the circulation appears to be regulated by thyrotropin (TSH)1 (7, 44). However, the mechanisms by which thyroglobulin crosses the closed follicular wall and reaches the circulation as an intact molecule are largely unknown.

Studies on the transepithelial passage of thyroglobulin require experimental access to the apical plasma membranes of the follicle cells. Suspension cultures of inside-out follicles prepared from pig thyroid glands provide a model for such studies (21). The wall of inside-out follicles is composed of a single layer of polarized thyroid epithelial cells: their apical plasma membranes are directed towards the culture medium and are separated by tight junctions from the basolateral cell surfaces that border the newly formed central cavity. Inside-out follicles are, therefore, well-suited to studies on the pathways of endocytosis exclusively from the apical plasma membrane (21).

In this study, evidence is presented that the pathways of endocytosis in epithelial cells of inside-out follicles include a transepithelial vesicular transport (transcytosis)2 from the apical plasma membrane into the basolateral plasma membrane.

1 Abbreviations used in this paper: CF, cationized ferritin; MEM, Eagle's minimum essential medium; and TSH, thyrotropin.

2 The term “transcytosis” was proposed by Simionescu (42) to denote the vesicular transport across endothelial cells. Transcytosis is not limited to the endothelium but also observed in numerous other cell types. It is synonymous with the formerly used terms “cytopempsis” (29) and “diacytosis” (24). The terms imply that substances are transmitted through the cytoplasm rather than utilized by the cell (29) and that this transport is carried out by vesicles that bypass the tight junctions and that couple endocytosis and exocytosis at different plasma membrane regions.
ical to the basolateral cell surfaces which is induced by TSH. These observations offer an explanation for the TSH-stimulated appearance of intact thyroglobulin in the circulation.

MATERIALS AND METHODS

Tissue

Thyroid glands from 335 pigs, 6–8 mo old (80–90 kg), were removed 5–10 min after anesthesia by electroshock and killing by bleeding. The glands were collected on ice and carried within 20 min to the laboratory for isolation of follicle segments.

Materials

Ruthenium red and dibutyryl cyclic AMP were obtained from Sigma Chemie GmbH, Munich, Federal Republic of Germany (FRG); TSH, from Ferring Arzneimittel GmbH (Kiel, FRG); and cationized ferritin (CF) with an isoelectric point at 8.5, from Miles Laboratories Inc., (Research Products Div., Elkhart, IN). Eagle’s minimum essential medium (MEM) with Earle’s salts was obtained from Boehringer GmbH (Mannheim, FRG); leucine-free MEM and fetal calf serum, from Grand Island Biological Co., Karlsruhe, FRG; and l-[4,5-3H]-leucine (specific activity 60 Ci/mmol) and [3H]toluene (2.4 Ci/g), from Amersham Buchler GmbH (Braunschweig, FRG). Acrylamide was obtained from SERVA Feinbiochemica GmbH & Co. (Heidelberg, FRG); and tetrachloroauric acid (HAuCl₄), from Merck AG (Darmstadt, FRG). Medical x-ray films (Curix RP 1) for fluorographic visualization of 3H-labeled thyroglobulin were obtained from Agfa Gevaert, Munich, FRG. For light and electron microscopic autoradiography, the L-4-emulsion from Ilford Ltd. (Ilford, Essex, England) was used.

Preparation of Inside-Out Follicles

Freshly collected glands were freed of the fibrous capsule and connective tissue and minced with razor blades into small pieces (~1 mm diam). Dissociation of tissue and isolation of intact follicle segments were performed as described previously (20). Within 24 h of suspension culture, the segments formed closed follicles whose epithelial cells exhibited, without exception, an inside-out polarity (21).

Application of Tracers for Studies on Endocytosis and Transepithelial Transport

Inside-out thyroid follicles were washed extensively in MEM to remove fetal calf serum which could interact with the tracers. The follicles used were either unstimulated or stimulated with TSH (50 mU TSH/ml or 60 μg dibutyryl cyclic AMP/ml) 10 min prior to the addition of the tracer.

CF AND MORPHOMETRIC ANALYSIS OF THE TRANSEPITHELIAL TRANSPORT: CF was added to the culture medium (10 μg/ml) which contained stimulated or resting follicles. 70-nm-thick Epon sections were prepared from follicles fixed 5–60 min after the addition of CF. Follicles with an average cell height of 10 μm were analyzed because they allowed a clear distinction between lateral and basal plasma membranes (Fig. 1). Follicles with attenuated epithelial cells as described by Wollman and co-workers (15, 32) were also observed but excluded from morphometric analyses because the lateral and the basal cell surfaces did not appear as structurally distinct domains. On electron micrographs with a final magnification of 12,000, the length of the basolateral membranes of the follicle cells was outlined with india ink and measured with a semiautomatic image-analyzing system MOP/AM 03 and incorporated microprocessor Z 80 (Kontron, Munich, FRG). All CF particles

![Figure 1](https://example.com/figure1.png)

**Figure 1** Portion of an inside-out follicle showing the polar organization of the epithelial monolayer. Ruthenium red adheres to the apical plasma membrane which is directed toward the culture medium. The stain does not penetrate the tight junctions (arrows). The margins between the basal cell surfaces (which border the newly formed central cavity) and the lateral plasma membranes are indicated by arrowheads. × 5,400.
FIGURE 2 Apical portion of an epithelial cell from a TSH-stimulated inside-out follicle, 60 min after the addition of CF to the culture medium. CF particles are seen on the apical plasma membrane (PM), in smooth surfaced endocytic vesicles (ve), in endosomes (ES, inset) where CF particles are attached to the inner surface of the membrane, in lysosomes (LYS; reached at ~5 min) where the tracer collects in the matrix, in stacked Golgi cisternae (G; reached at ~30 min), and on the lateral plasma membrane (reached at ~11 min; arrows). N, nucleus; zo, zonula occludens. × 56,000; inset, × 65,000.

THYROGLOBULIN-GOLD CONJUGATE: For isolation of 19-S-thyroglobulin, the technique of Rolland and Lisitsky (38) was used with some modifications. Pig thyroid glands were freed of connective tissue and minced into small (1 mm) tissue fragments. 10 g of tissue fragments was suspended in 100 ml of MEM and stirred with a magnetic rod for 4 h at 4°C. The suspension was filtered through a 200-μm nylon gauze and the filtrate was centrifuged for 30 min at 40,000 g at 4°C with a SW 28 rotor in a Beckman ultracentrifuge.

associated with the basal and the lateral plasma membranes were counted on electron micrographs with a magnification of 48,000 using a binocular Leitz-Wild stereomicroscope M3 with a working distance of 26.5 cm (Leitz, Munich, FRG). For each time point, nine cells from two independent experiments were analyzed. Data are based on a total of 12,000 CF particles from 180 follicle cells and expressed as number of CF particles per micrometer basolateral plasma membrane length. The numbers of CF particles in the very narrow intercellular clefts were divided by 2 because both neighboring cells contribute to the extracellular accumulation of the tracer.

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FIGURES 3 and 4  Transcytosis of CF. Endocytic vesicles fuse first (beginning at ~11 min) with the lateral plasma membrane (Fig. 3) and 5 min later, at ~16 min, with the basal cell surface (Fig. 4). Exocytotic pits carry a coat on their cytoplasmic surfaces (arrows). Fig. 3, x 136,000; Fig. 4, x 114,000.

Gold particles with an average diameter of 20 nm were prepared by reduction of HAuCl₄ with Na-citrate as described by Frens (4). 10 ml of colloidal gold (~10¹⁴ particles/ml [22, 49]) and 200 µl of freshly prepared thyroglobulin (2.4 mg or 2.15 x 10¹⁵ thyroglobulin molecules) containing 10 mM EDTA were rapidly mixed. The mixture contained ~400 times more thyroglobulin molecules than gold particles. The solution (pH 5.0) was gently shaken for 2 h at room temperature and then centrifuged through a 40% sucrose cushion, pH 7.5, for 60 min at 50,000 g at 15°C (Beckman SW 28 rotor, Beckman Instruments, Inc.). This resulted in a loose layer of gold particles at the bottom of the tube. The stable conjugate could be stored at 4°C for at least one week. Thyroglobulin-gold conjugates were added to the follicles (which were washed extensively in MEM before use) to yield a final concentration of ~10⁻⁶ conjugates/ml. This corresponds to ~0.3 µg thyroglobulin/ml because most gold particles carry three thyroglobulin molecules (see Results). Usually, the thyroglobulin-gold conjugates remained stable when added to inside-out follicles suspended in MEM. Occasionally, however, aggregation of conjugates was observed; such preparations were discarded. Samples of follicles were removed during incubation in the radiolabeled solutions after 5, 30, 60, and 300 min and prepared for electron microscopic autoradiography.

Electron Microscopy

Samples of inside-out follicles were fixed in Karnovsky’s fixative (25) for 2 h at room temperature, pelleted in a Microfuge (Beckman Instruments Inc.), postfixed in 1% unbuffered OsO₄ for 1 h at 4°C, and embedded in Epon. Thin sections were cut with diamond knives, stained with lead citrate, and examined in a Siemens Elmiskop I or 102 (Siemens AG, Munich FRG) at 80 kV.

Ruthenium Red: Staining with ruthenium red has been used primarily for cytochemical visualization of anionic sites, e.g., on the glycocalyx (28). It has also been useful for demonstrating the tightness of an epithelial wall by its

The values are based on the molecular weight of thyroglobulin, Mr = 660,000 (9) and the number of molecules per mole, N_{molar} = 6.023 x 10²³ X mol⁻¹.
FIGURE 5 Effect of stimulation with TSH on the transepithelial appearance of CF. In the presence of TSH, the number of CF particles on the basolateral plasma membrane is about ninefold that of resting cells (no TSH). Bars represent mean values from nine cells ± SD.

failure to penetrate the junctional complex (39). Ruthenium red was applied either without purification or after recrystallization (13). A 0.5% aqueous solution was sonicated (Branson Sonic Power Co., Danbury, CT) at 25°C for 5 min. Inside-out follicles were resuspended at room temperature for 5–60 min in a medium containing 1.2% glutaraldehyde and 0.1% ruthenium red in 0.15 M sodium cacodylate, pH 7.3 (28), postfixed in 1% unbuffered OsO₄ at 4°C and prepared for electron microscopic observations as described above. The best staining of the apical glycocalyx was obtained with freshly prepared solutions of recrystallized ruthenium red.

AUTORADIOGRAPHY: 70-nm Epon sections were coated with Ilford-L4-emulsion using the flat substrate technique of Salpeter and Bachmann (40), exposed at 4°C for 10 d, and developed in Kodak D-19.

For morphometric quantitation of the transepithelial appearance of [³H]thyroglobulin, light microscopic autoradiographs were analyzed at a magnification of 400. The boundary between the cell bases and the central cavity of inside-out follicles was outlined and the number of silver grains was related to the area of the central cavity. 20 follicles were analyzed after stimulation with TSH and after 1 and 5 h of exposure to [³H]thyroglobulin. Results are based on a total number of 1,800 silver grains and expressed as mean density = grains X mm⁻².

NEGATIVE STAINING: Thyroglobulin or the thyroglobulin-gold conjugates were suspended in PBS containing 10 mM EDTA, and stabilized by the addition of 0.02% glutaraldehyde. Negative staining was performed with 2% uranyl acetate, pH 5.

RESULTS
Follicle segments isolated from pig thyroid glands formed closed follicular structures in which the apical plasma mem-
with dibutyryl cyclic AMP. Endocytosis and the vesicular transport to the lateral and the basal cell surfaces decreased by ~80% by lowering the temperature of the incubation medium to 25°C. Transcytosis of CF ceased at 15°C and below (Fig. 6), concomitant with a stop of endocytosis at the apical plasma membrane. After 16 min of endocytosis and at all time points thereafter, even at 25°C, the number of CF particles on the basolateral plasma membrane was always two to three times greater than that on the basal cell surface.

**Endocytosis of the Colloidal Gold-Thyroglobulin Conjugate**

Pig thyroglobulin is an ovoid molecule measuring about 30 × 15 nm (Fig. 7), similar to the thyroglobulin of man (1), and of other mammalian species, whereas colloidal gold had a mean particle diameter of 20 nm. The gold particles were usually surrounded by three thyroglobulin molecules; occasionally, one gold particle was associated with only two or with more than three (Fig. 7). Colloidal gold-thyroglobulin conjugates adhered to the apical plasma membrane (Fig. 8) whereas gold particles alone did not. Attachment of gold-thyroglobulin conjugates to the apical plasma membrane was inhibited by an excess of free, nonconjugated thyroglobulin (5 mg/ml). In follicle preparations stimulated with TSH, the conjugates were internalized and reached the lysosomes within 5 min (Fig. 9). Conjugates were never observed in stacked Golgi cisternae (Fig. 9). Beginning at 30 min, but occasionally already at 15 min, gold-thyroglobulin conjugates were released at the basolateral cell surface into the central cavity (Figs. 10 and 11). Apparently, gold-thyroglobulin conjugates were carried transcellularly by small (100–200 nm) vesicles which released their content by exocytosis (Fig. 10).

As in the case of CF, the membrane of exocytotic pits carried a coat on its cytoplasmic surface (Fig. 10). The transepithelial transport of gold-thyroglobulin conjugates was observed only after stimulation with TSH but not in resting follicles. Gold particles did not remain attached but dissociated from the basolateral plasma membrane. Whether thyroglobulin remained attached to the gold particles after passage through the epithelial monolayer cannot be decided at present.

**Endocytosis of [3H]Thyroglobulin**

[3H]Thyroglobulin was synthesized and released into the culture medium by inside-out follicles after incubation with [3H]leucine. [3H]Thyroglobulin (Fig. 12b) showed the same mobility in SDS PAGE as the 19-S-thyroglobulin (Fig. 12a) prepared by precipitation with ammonium sulfate from unlabeled pig thyroid tissue. Newly synthesized and released [3H]thyroglobulin was concentrated and added to freshly prepared and TSH-stimulated inside-out follicles. Autoradiography revealed silver grains along the apical plasma membrane and, within 5–15 min of endocytosis, over lysosomes (Fig. 13). After 30 min of endocytosis, silver grains became visible over the intercellular clefts (Fig. 14) and the central cavity (inset Fig. 14). No silver grains were observed over stacked Golgi cisternae. Light microscopy and morphometric analysis of silver grains after 1 and 5 h of endocytosis showed that the grain density over the central cavity increased with time (Fig. 15). Silver grains did not accumulate over the central cavity when follicles were exposed to [3H]thyroglobulin at 4°C.

**DISCUSSION**

Under appropriate culture conditions, follicle segments isolated from pig thyroid gland form closed follicular structures...
Ficures 8 and 9  Adherence of thyroglobulin-gold complexes to the apical plasma membrane of inside-out follicles (Fig. 8). After 5 min of endocytosis, gold particles become visible intracellularly in the matrix of lysosomes. After 60 min, most lysosomes are labeled (LYS, Fig. 9). Note the absence of particles in stacked Golgi cisternae (G, Fig. 9). Fig. 8, x 31,500; Fig. 9, x 35,000.

In which all epithelial cells exhibit a stable inside-out polarity (21). The tightness and the reversed polarity of the epithelial wall are prerequisites to the study of endocytosis exclusively from the apical cell surface.

Based on observations with single follicle cells and with thyroid slices, it has been assumed that receptors are present on the cell surface which recognize asialothyroglobulin (6), and that a preferential uptake of the highly iodinated thyroglobulin species occurs (46). The experiments with inside-out follicles have shown that thyroglobulin-gold conjugates and [3H]thyroglobulin are indeed attached to the apical cell surface, thus supporting the view that binding sites for thyroglobulin exist on the plasma membrane and that internalization occurs with a certain selectivity (6, 46).

Pathways of Endocytosis to Lysosomes and to the Golgi Complex

Previous studies on follicle cells in situ have shown a rapid transfer of tracers and of thyroglobulin to endosomes and lysosomes (41) where thyroid hormones are liberated by proteolysis of thyroglobulin (45, 50). In inside-out follicles, endocytosis of CF is followed by the transfer to lysosomes within 5 min (21). Endosomes are prelysosomal compartments (17)
which are reached by the tracer earlier than lysosomes and which form an intermediate station along the lysosomal pathway. The participation of the Golgi complex in endocytosis has been interpreted in the thyroid (20, 21) and in other secretory cells (11, 19, 33; for reviews see 12, 18) as an indication of reutilization of internalized plasma membrane during the secretory process. After 30 min of endocytosis, Golgi cisternae become labeled with CF but not with anionic markers such as thyroglobulin-gold conjugates as shown here or with native ferritin as previously shown (20). This differential labeling of Golgi cisternae suggests a separation of the pathways for thyroglobulin and native ferritin (which are anionic) and for cationized ferritin. The importance of the net charge of the tracer for the routes taken by endocytic vesicles was first pointed out by Farquhar (11): In anterior pituitary cells, vesicles carrying native (anionic) ferritin fuse only with elements of the lysosomal system, whereas vesicles with cationized ferritin can also fuse with Golgi cisternae. In
The height of thyroid follicle cells determine the time required for transcytosis.

Transcellular transport has also been detected in the rat choroid epithelium by the use of CF (47), in intestinal epithelial cells of neonatal rats that transport IgG (5, 35), and in glandular epithelial cells (5, 30) and hepatocytes (34) that translocate IgA molecules. Apparently, the transcellular vesicular transport is a common pathway and is also found in some secretory epithelial cells.

Preliminary morphometric analyses showed that after 1 h of endocytosis ~9% of all internalized CF particles were transported to the basolateral plasma membranes. This corresponds to ~18% of all CF particles found in lysosomes. Hence, transcytosis in thyroid follicle cells is an endocytic pathway of considerable proportion; it requires mechanisms that compensate for the membrane flow from the apical to the basolateral cell surfaces. A vesicular transport in the opposite direction has been observed in rightside-out follicles of rat thyroid gland with CF as tracer (8). It is unknown at present whether the rate of membrane flow of one pathway relates to that in the opposite direction.

It is of interest that not only CF as a nonspecific membrane marker but also small fractions of internalized thyroglobulin are transported through the follicle cell. Most internalized thyroglobulin is transferred first to lysosomes and it cannot be ruled out that endocytic vesicles fuse intermittently with lysosomes and detach again before being inserted into the basolateral plasma membranes. However, recent observations indicated that the transcellularly transported thyroglobulin escapes the lysosomal degradation because [3H]thyroglobulin used as a tracer has the same electrophoretic mobility before and after transcytosis (unpublished observations). It is more likely, therefore, that transcytotic vesicles derive directly from the apical cell surface and bypass the lysosomal compartments.

The experiments with [3H]thyroglobulin and with thyroglobulin-gold indicated that thyroglobulin detaches from the basolateral cell surfaces after transcytosis. In absorptive intestinal cells, it has been observed by Rodewald (36) that binding of IgG immunoglobulins to the luminal cell surface and their detachment from the basolateral cell surface after transepithelial transport are pH-dependent. Nothing is yet known about how the detachment of thyroglobulin from the basolateral cell surfaces is regulated.

For the release of thyroglobulin from follicles in situ, mechanisms other than transcytosis have been discussed in the past: (a) inflammation of the thyroid (e.g., subacute thyroiditis) which leads to destruction of the parenchyma and leakage of follicular constituents into the circulation (48); (b) temporary relaxation of tight junctions which would cause extracellular diffusion of thyroglobulin from the follicular lumen (48); and (c) exocytotic release of newly synthesized thyroglobulin also on the basolateral cell surfaces (23), which would imply that no functional polarity of thyroid follicle membranes exists. The three alternative mechanisms for the release of thyroglobulin in situ do not operate in the in vitro system of inside-out follicles, because the epithelial wall retains its inverse structural and functional polarity and remains intact and sealed against extracellular leakage even during stimulation with TSH.

The observations with CF and with thyroglobulin as tracers of endocytosis lead to the conclusion that a transepithelial vesicular transport is established in thyroid follicle cells which...
Endocytosis and transepithelial transfer of tritiated thyroglobulin that was previously synthesized and released by another preparation of inside-out follicles in the presence of tritiated leucine (see Fig. 12). Silver grains are visible over the apical plasma membrane (Fig. 13) and, beginning at ~5 min, over lysosomes (LYS, Fig. 14). Beginning at ~30 min, silver grains become visible also over the intercellular clefts (Fig. 14) and the central cavity where their number increases with time. This is best observed in light microscopic autoradiographs (inset Fig. 14, after 5 h of endocytosis). Fig. 13, ×16,000; Fig. 14, ×18,000; inset, ×580.
bypasses the tight junctions and, possibly, the lysosomal compartment and which is controlled by TSH. It is presumed that transcytosis of thyroglobulin occurs also in follicle cells in situ and that it accounts for the appearance of thyroglobulin in the circulation.

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