Targeting of Big Stanniocalcin and Its Receptor to Lipid Storage Droplets of Ovarian Steroidogenic Cells*

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Stanniocalcin (STC) is a large polypeptide hormone that is widely distributed in tissues such as kidney, adrenal, and ovary. In most tissues, STC exists as a 50-kDa homodimer (STC	extsubscript{50}). The ovaries produce a higher molecular weight variant (big STC) in androgen-producing theca cell and interstitial cell compartments. Luteal cells, which do not express the STC gene, nonetheless contain high levels of STC protein, suggesting they are targeted by and sequester big STC through a receptor-mediated process. Recently, an STC/alkaline phosphatase fusion protein was used to characterize mitochondrial targeting and sequestration of STC	extsubscript{50} and its receptor in liver and kidney. The main objective of the present study was to characterize big STC and its receptor in mammalian ovary and determine whether the ovarian STC variant was similarly targeted to luteal cell mitochondria. By in situ ligand binding, we identified large numbers of STC receptors on corpus luteal cells. However, a more detailed analysis of sub-cellular fractions revealed that both STC and its receptor were not preferentially targeted to mitochondria but instead to cholesterol/lipid storage droplets, which was more indicative of a role in steroidogenesis. Functional studies revealed that additions of big STC had concentration-dependent inhibitory effects on both basal and stimulated progesterone output by primary cultured luteal cells. Furthermore, STC receptor levels were up-regulated in luteal cells in response to protein kinase A activation. Taken together, these findings indicate that theca cell-derived big STC is targeted to the cholesterol/lipid storage droplets of luteal cells to regulate steroidogenesis. This constitutes the first reported description of polypeptide hormone and receptor targeting to cholesterol/lipid droplets and the first biological role for the big STC variant.

The hormone stanniocalcin (STC)\textsuperscript{1} is widely distributed in mammalian tissues and for the most part functions locally, because STC is not normally found in the blood. In most tissues, STC exists as a 50-kDa homodimer known as STC	extsubscript{50}. This form of the hormone has a unique signaling pathway whereby it is heavily sequestered by its target cells. In liver and kidney, for instance, STC	extsubscript{50} is first sequestered by target cells and then traffics to their mitochondria where it increases the rate of electron transport. Because STC receptors are present on both the plasma membranes and the mitochondria of target cells, the whole process appears to be receptor-mediated.

By far the highest levels of STC gene expression are observed in the ovary (1), where the transcript is confined to theca and interstitial cells (TIC). Interestingly, STC protein is found not only in TICs but also in oocytes and cells of the corpus luteum (1), suggesting that the STC is produced by TICs for targeting to oocytes and luteal cells. The fact that the protein is readily detectable in cells that do not make the hormone further suggests that, as in the case of STC	extsubscript{50} signaling in liver and kidney (2), ovarian STC is also sequestered by its target cells. An important question here is whether or not ovarian STC undergoes the same mitochondrial targeting as observed in liver and kidney. Central to this question is the recent discovery that ovarian STC is structurally different from the 50-kDa homodimer found in most other tissues. Big STC, as we have named the ovarian STC variant, consists of three higher molecular mass species of 84, 112, and 135 kDa, that appear to be oligomeric complexes of a larger STC monomer (3).

The ability of luteal cells to sequester STC to an extent readily detectable by immunocytochemistry (1, 4) implies the presence of STC receptors and/or binding proteins in these cells. In this regard, we recently used an STC/alkaline phosphatase (AP) fusion protein (STC/AP) to characterize receptors and delineate the mitochondrial targeting of STC	extsubscript{50} in liver and kidney (2). The objective of this study, therefore, was to use the same methodology to characterize STC receptors in ovarian luteal cells and thereby address the question as to whether or not big STC is similarly targeted. Our findings have revealed that, in addition to being structurally unique, big STC has a novel trafficking pathway in regulating luteal cell function. As a result, we have uncovered a novel targeting pathway for polypeptide hormones.

EXPERIMENTAL PROCEDURES

Reagents—Bovine serum albumin, forskolin, and 1,9-dideoxyforskolin were obtained from Sigma. Collagenase type II and Medium 199 were purchased from Invitrogen. DNase type I was procured from Roche Applied Science, and UltraCulture media were obtained from BioWhittaker (Walkersville, MD). Rabbit anti-progesterone anti-serum was a gift from Dr. T. G. Kennedy (University of Western Ontario, London, Ontario).

Hormone Purification—Big STC was purified from conditioned media by immunoaffinity column chromatography. This entailed the prep-
aparation of an STC immunoaffinity column by coupling the IgG fraction from a polyclonal human STC antiserum to CNBr-Stepharose 4B (Amersham Biosciences) as described previously (5). Conditioned media (24 h) from HT1080 cells, a human fibrosarcoma cell line that secretes big STC (3), was then recycled through the column overnight. Bound big STC was eluted with 0.1 M glycine, pH 3, containing 0.5 M sodium chloride. The elution profile was monitored by RIA for STC content. The relevant fractions were pooled, concentrated, and buffer-exchanged on a Centricron YM-10 centrifugal filter device (Millipore). The STC content of the concentrate was then quantified by RIA prior to use.

**Bovine Luteal Cell Cultures**—Bovine ovaries were obtained from a local abattoir. The corpora lutea were removed and washed several times in Hank's balanced salt solution containing 0.1% bovine serum albumin. An enriched/highly pure population of dispersed bovine luteal cells (BLCs) was obtained by mincing the isolated corpus luteum and subsequently digesting the tissue in an enzymatic mixture of collagenase type II and DNase I as described previously (6, 7). Bovine luteal cell viability was assessed by trypan blue exclusion. Cells were seeded at a density of 500,000 cells/ml in 24-well tissue culture plates and maintained at 37 °C in UltraCulture media supplemented with an antibiotic-antimycotic solution (Invitrogen). The proportion of steroidogenic BLCs was monitored by 3α-hydroxysteroid dehydrogenase (3βHSD) enzyme histochemistry as described previously (8). The ability of the luteal cells to respond to hormone stimulation was assessed by measuring the accumulation of progesterone in the culture medium in response to luteinizing hormone (LH).

**Western Blot Analysis**—Intracellular luteal cell protein and conditioned cell culture media were obtained as described previously (3). Protein concentrations were standardized using the Bio-Rad protein assay kit. Following SDS-PAGE, proteins were transferred to polyvinylidene difluoride membranes (Roche Applied Science) and incubated with polyclonal hSTC antiserum (1:40,000) followed by horseradish peroxidase-conjugated donkey anti-rabbit antibody (1:50,000; Amersham Biosciences) and subsequently developed with an ECL Western blotting detection kit (Amersham Biosciences).

**Receptor Binding Assays/Receptor Localization**—In situ ligand binding and receptor binding assays were performed on whole luteal cells and purified plasma membranes as described previously using an STC-AP fusion protein (2). Receptor binding studies were also performed on cholesterol/lipid storage droplet (CLD) isolates from bovine corpus luteum (9). These assays were conducted as described previously for plasma membranes, except that tubes were periodically vortexed to prevent the separation of aqueous and non-aqueous phases. Following centrifugation, free and CLD-bound STC-AP fusion proteins were separated by aspiration of the infranatant with a 23-gauge needle. AP assay buffer was then added to the remaining supernatant containing the CLD fraction, and AP activity was detected as described previously (2).

**Radioimmunoassay**—Sub-cellular fractions of the bovine corpus luteum and conditioned media collected from cultured luteal cells were analyzed by RIA as described previously (3).

**Immunohistochemistry**—Double-label immunofluorescence microscopy was used to co-localize STC and perilipin in sections of mouse ovaries. Ovaries were fixed in 4% paraformaldehyde and sectioned as described previously (10). Sections were then co-incubated with rabbit anti-STC (1:1000) and goat anti-perilipin (1:1000) anti-serum overnight. Donkey anti-rabbit rhodamine-IgG and mouse anti-goat fluorescein isothiocyanate-IgG were used to visualize the STC and perilipin antigens using a confocal microscope (Bio-Rad Radiance 2000 laser scanning system).
results of recent studies in liver and kidney in which large numbers of specific high affinity receptors for STC in all three preparations. STP AP fusion protein. Fig. 1, shows that the strongest STP AP binding is typically in tissue sections of adult mouse ovary using the STP AP fusion protein. Fig. 1, A and B show that the strongest STP AP binding was evident in the oocytes of primary and secondary follicles and in a sub-population of cells in the corpus luteum, as indicated by the deep purple color. The staining in luteal cells was noticeably punctate in appearance, whereas that in these cells. Proteins were resolved on a 10% acrylamide gel under non-reducing conditions. High molecular mass big STC (84, 112, and 135 kDa) present in total bovine luteal cell extracts as well as in the proteins extracted from the lipid storage droplets of these cells. Proteins were resolved on a 10% acrylamide gel under non-reducing conditions.

**STC Receptor Localization in Cultured Luteal Cells**—In view of the strong STP AP fusion protein binding to luteal cells in tissue sections, in situ ligand binding was also conducted on isolated luteal cells following acetone fixation. We used well established techniques to isolate highly pure and functional BLCs (6, 7). Routinely, >85% of the cells were steroidogenically active as indicated by 3β-hydroxysteroid dehydrogenase enzyme biochemistry, and their progesterone output was significantly enhanced in response to hCG stimulation, indicating that they were fully functional cells (results not shown). As in the case of tissue sections, plated cells exhibited strong STP AP binding, indicative of a high number of STC receptors. Furthermore, the staining in freshly isolated cells was also punctate in appearance (Fig. 1E), as seen with luteal cells in ovarian tissue sections.

**Receptor Binding Studies**—Saturation binding studies on isolated luteal cells and their membranes yielded high affinity binding sites in both instances. Receptors on whole cells had an estimated $K_d$ of 1.5 nM with a $B_{max}$ of 5 pmol/mg protein (Fig. 2A). This was similar to the $K_d$ of 1.2 nM and a $B_{max}$ of 8 pmol/mg protein for isolated plasma membranes (Fig. 2B). The possibility that receptors might reside in a sub-cellular compartment was evident from the punctate staining obtained by in situ ligand binding. This notion was also based on our recent studies in liver and kidney in which large numbers of cellular STC receptors were revealed on both the plasma membranes and mitochondria. We therefore proceeded to examine this possibility in the ovary by determining the sub-cellular distribution of STC receptors in luteal cells. The results re-
revealed that there was little binding activity in the nuclear and mitochondrial fractions from the corpus luteum, whereas significant binding activity was observed in the CLD fraction. Here, saturation binding studies revealed the presence of a high affinity receptor with an estimated $K_d$ of 0.2 nM and a $B_{\text{max}}$ of 25 pmol/mg protein (Fig. 2C). In contrast to hSTC, competition binding studies with 10 μM follicle-stimulating protein (FSH), hCG, luteinizing hormone-releasing hormone (LHRR), and STC-related protein (STCrP) produced no measurable displacement of STP-AP, thus demonstrating the specificity of STP-AP binding to the CLD fraction.

**Sub-Cellular Distribution of Ovarian STC**—Because of the presence of significant binding activity on both plasma membranes and the CLD fraction, and because STC$_{\text{bop}}$ is known to be heavily sequestered by target cell mitochondria (2), we proceeded to examine the sub-cellular distribution of the ligand. As in the case of liver and kidney, some STC immunoreactivity was detected in the 10,000 × g mitochondrial fraction (−7%; 3.3 ng of STC/mg of total mitochondrial protein). However, the majority of STC immunoreactivity resided in the cytoplasm (−89%; 41.5 ng of STC/mg of protein), and none was detected in the nuclear (1000 × g) or plasma membrane fractions (100,000 × g). Further fractionation of the cytosol into aqueous and lipid components revealed that most intra-cellular STC (−75%; 111.1 ng of STC/mg of CLD protein) was localized to the CLD fraction where we also observed significant receptor binding activity.

Western blot analysis confirmed the RIA data on the luteal cell sub-cellular fractions by demonstrating that STC was only detectable in the CLD fraction. In contrast to previous studies (2), STC was undetectable in luteal mitochondria and plasma membranes (400 μg of protein/lane; Fig. 3A), however a further sub-cellular fractionation revealed that STC was present in the CLD fraction. Furthermore, as in the case of theca cells, luteal cells only contained the higher molecular mass big STC variant (Fig. 3B). These findings then prompted us to determine whether this novel sub-cellular distribution was unique to luteal cells or was a feature of all ovarian steroidogenic cells. Interestingly, RIA analysis of sub-cellular fractions from purified bovine theca cells yielded similar results, revealing that big STC in theca cells was also preferentially confined to the CLD fraction (results not shown).

To further validate our RIA and Western blotting data, fluorescence microscopy was employed to co-localize big STC with perilipin, a protein that is uniquely localized to the membrane of CLDs in steroidogenic cells (9). As shown in Fig. 4, most luteal cells that were immuno-positive for perilipin (Fig. 4B, green fluorescence) were also positive for STC (Fig. 4A, red fluorescence), resulting in a high degree of overlap (Fig. 4C, orange fluorescence). A similar pattern of STC and perilipin distribution was observed in follicles. As expected, a high degree of STC immunoreactivity was observed in theca cells and oocytes (Fig. 4D, red fluorescence). Those theca cells, which were STC immunopositive, also contained high levels of immunoreactive perilipin (Fig. 4E, green fluorescence), resulting in a high degree of overlap (Fig. 4F, orange fluorescence). There was no co-localization of STC and perilipin in oocytes, suggesting that here the ligand likely resides in a different sub-cellular compartment.

Receptor Regulation—Having characterized luteal cell STC receptors, we proceeded to examine whether they were susceptible to regulation. To this end we employed cultured BLCs and subjected them to treatment with ovarian steroids as well as various signal transduction pathway activators. As shown in Fig. 5, binding activity was consistently up-regulated significantly only in response to forskolin, an activator of adenylate cyclase. Receptor levels were not affected by treatment with sex steroids relevant to the ovary (progesterone, estradiol-17β, androstenedione; all tested at 0.01–10 μM), the glucocorticoid dexamethasone (0.01–10 μM), or hCG (100 ng/ml).

**Effects of STC on Progesterone Secretion**—Finally, we addressed the possible role of big STC in luteal cell function. Because progesterone is the primary steroid produced by luteal cells, and given the association of ovarian STC with the CLD, we elected to examine the effects of big STC on steroid output. As shown in Fig. 6A, progesterone secretion by cultured BLCs was reduced significantly in cultures treated with big STC as compared with controls ($p < 0.01$), suggesting that big STC has regulating effects on luteal cell progesterone secretion. This inhibitory effect of big STC on luteal cell progesterone secretion was attenuated with the addition of STC anti-serum (Fig. 6B).

Moreover, big STC also inhibited hCG-stimulated progesterone ($P_4$) release in addition to basal progesterone release (Fig. 6C). The addition of hCG alone (0.01–100 ng/ml) had concentration-dependent stimulating effects on progesterone output (−40 ng/ml in control cultures to −150 ng/ml in maximally stimulated cells). The addition of big STC decreased basal progesterone secretion but, more importantly, inhibited hCG-stimulated progesterone secretion at all concentrations tested (0.01–100 ng/ml).

**DISCUSSION**

Previous studies have described obvious discordances in the patterns of STC mRNA and protein distribution in mammalian tissues. During kidney development, for instance, STC gene expression is confined to undifferentiated mesenchymal cells, whereas the STC protein is equally abundant in adjacent nephron cells undergoing terminal differentiation (11). Simi-
larly, in adult kidney the STC gene is uniquely expressed in collecting duct cells, whereas STC immunoreactivity is equally evident in other nephron segments. These findings have led us to formulate a sequestering hypothesis of STC action whereby STC is produced and released by one cell type and sequestered by adjacent target cells (12). This hypothesis has now been proven in the case in the kidney, where it has been shown that collecting duct-derived STC is heavily sequestered by target cell mitochondria via a receptor-mediated process in order to stimulate electron transport (4).

The sequestering phenomenon is not unique to kidney. Liver mitochondria contain equally high levels of both ligand and receptor and, more to the point, the same discordant pattern of mRNA and protein distribution has also been described in mammalian ovary. In both the mouse and the bovine ovary, the STC gene is solely expressed in TICs, whereas oocytes and corpus luteal cells contain equally high levels of the ligand (1, 3). However, because TICs produce a higher molecular weight form of the hormone, the compelling question in the case of the ovary has always been whether or not the hormone is sequestered by the same sub-cellular compartment. In addressing this question, the present study has now revealed that big STC does in fact have a unique sub-cellular targeting pathway.

Our initial analysis of luteal cell sub-cellular fractions revealed measurable albeit low levels of STC in mitochondria. However, most of the STC was confined to the cytoplasm, and the majority of this was associated with the CLD fraction where it co-localized with perilipin, indicating that big STC is distinct both structurally and in its sub-cellular targeting. To determine whether this CLD targeting of the ligand was receptor-mediated, we analyzed the sub-cellular distribution of receptors by employing the same STP/H18528AP fusion protein technology that was used to characterize mitochondrial receptors in rodent liver and kidney (2). The results revealed that this was indeed the case. In situ ligand binding demonstrated high concentrations of receptors in a sub-population of large and small luteal cells. Furthermore, the majority of ligand binding was cytoplasmic and punctate in appearance, as if confined to a specific organelle. This was confirmed by classical binding assays in which significant populations of receptors were identified in the CLD fraction in addition to plasma membranes. To our knowledge, this is the first reported instance of polypeptide hormone and receptor targeting to the CLD fraction of any steroidogenic cell. The properties of the membrane-associated

FIG. 5. Luteal cell STC receptor regulation. Cultured luteal cells were exposed to treatments as indicated for 24 h. Receptor binding assays were then performed as described under “Experimental Procedures.” As shown in panel A, STC receptor levels in luteal cells were not affected by treatment with hCG (100 ng/ml), estradiol, dexamethasone, or androstenedione (10^-6 M). As shown in panel B, however, in response to forskolin, STC receptor levels consistently increased in stepwise fashion, whereas the forskolin analog, 1,9-dideoxyforskolin, had no effect. Shown are representative data from one experiment that was conducted at least two times. Each bar represents the mean ± S.E. of three replicates. Asterisk (*) denotes p < 0.01 compared with control (analysis of variance/Dunnett’s test).

FIG. 6. Effect of big STC on luteal cell progesterone production. A, cultured luteal cells were incubated in UltraCulture media with or without immunopurified big STC for 24 h. The progesterone accumulation in the media was then assessed by RIA. B, STC caused a significant decrease in luteal cell progesterone secretion, an effect that could be abolished with STC antiserum in control and STC-treated cultures. C, luteal cells were also maintained in UltraCulture media containing increasing concentrations of hCG (0.01–100 ng/ml) with or without ovarian STC (0.3 nM) for 24 h. Progesterone accumulation in the culture media was then assessed by RIA. As expected, hCG dose-dependently stimulated progesterone release, which was then inhibited by STC. Each bar represents the mean of at least three replicates; asterisk (*) indicates p < 0.001.
receptor were similar to those reported for liver and kidney (2).

In contrast to adipocytes which only contain a single fat droplet, steroidogenic cells contain numerous smaller CLDs dispersed throughout the cytoplasm. These droplets are surrounded by a single phospholipid layer or microenvironment (membrane versus CLD). For instance, plasma membrane-associated carbohydrate moieties such as heparin sulfate proteoglycans are known to dramatically affect ligand-receptor interactions for several members of the fibroblast growth factor family (30, 31). However, perhaps the more important question is why a higher affinity receptor is necessary on the lipid droplets. At the present time, the only possibility that comes to mind is that it serves as a high affinity "trap" to ensure a very high degree of ligand sequestration by the CLD fraction, which is obviously required for this unique brand of signaling.

In conclusion, this report is the first description of receptor-associated, polypeptide hormone targeting to the membrane of cholesterol/lipid storage droplets. In doing so, we have also described for the first time a biological role for the big STC variant, namely in the negative regulation of progesterone production. Lastly, we have succeeded in identifying both big STC and STC receptors in luteal cells, thereby providing credence to the sequestering hypothesis within the ovary whereby luteal cells sequester the TIC-derived hormone through a receptor-mediated process. There is much that remains to be done before we fully understand the underlying mechanisms of STC-regulated steroidogenesis, but the results presented here should serve as a foundation for future investigations.

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