Regulation by Adrenocorticotropic Hormone of the in Vivo Expression of Scavenger Receptor Class B Type I (SR-BI), a High Density Lipoprotein Receptor, in Steroidogenic Cells of the Murine Adrenal Gland*

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The class B, type I scavenger receptor, SR-BI, binds high density lipoprotein (HDL) and can mediate selective uptake of HDL cholesteryl esters by cultured cells. The high levels of expression of SR-BI in steroidogenic tissues and the importance of selective uptake of HDL as a source of cholesterol for steroidogenesis raised the possibility that SR-BI may participate in cholesterol delivery to steroidogenic tissues in vivo. We have used immunoblotting and immunohistochemical methods to show that SR-BI is specifically expressed in a distinctive pattern on the surfaces of steroid-producing cells in the murine adrenal gland's cortex and that its expression in vivo is induced by adrenocorticotropic hormone and suppressed by glucocorticoids. Thus, expression of SR-BI protein is coordinately regulated with adrenal steroidogenesis. These data provide strong support for the hypothesis that SR-BI is a physiologically relevant HDL receptor that provides substrate cholesterol for steroid hormone synthesis.

The intercellular transport of lipids, including cholesteryl esters and triglycerides, through the blood involves their packaging into water-soluble lipoproteins and the targeted delivery of lipoprotein lipids to cells via receptor-mediated processes (1). The best understood of the lipoprotein transport systems is the LDL1 receptor pathway of receptor-mediated endocytosis. LDL binds to its surface receptor, is internalized via coated pits, and the entire lipoprotein particle is subsequently degraded in lysosomes to release free cholesterol to the cell. HDL also delivers cholesterol to cells through a well defined process called selective cholesterol uptake (2–12). HDL particles bind to surface receptors on target cells, their cholesteryl esters are selectively transferred into the cells without the degradation of the lipoprotein particle, and the lipid-depleted esters including their two major apolipoproteins, apoA-I and apoA-II, are released from the cells, a process that is fundamentally different from the endocytic uptake of lipoproteins mediated by members of the LDL receptor family.

The HDL-cholesteryl ester selective uptake pathway occurs in cultured hepatocytes and in the liver (3, 4, 7–9, 11, 12), where it may contribute to the clearance of plasma cholesteryl ester in the terminal stage of reverse cholesterol transport (13, 14). The HDL selective uptake pathway plays a prominent role in cholesterol delivery to steroidogenic cells of mice and rats where it appears to be responsible for the overwhelming majority of the uptake of HDL cholesteryl (3, 4, 6, 8, 12). Indeed, HDL is significantly more effective than LDL in supplying cholesterol for cholesteryl ester accumulation and corticosterone production in adrenal glands of rats and mice (5, 15–17). Using gene knockout mice, Plump et al. (18) showed that apoA-I deficiency caused an almost complete failure to accumulate cholesteryl ester in steroidogenic cells of the adrenal gland, ovary, and testis, a result illustrating the importance of HDL-apoA-I, presumably via its role in the selective uptake pathway, for cholesterol homeostasis in steroidogenic cells. HDL has also been reported to be a source of cholesterol for steroidogenesis in cultured human adrenal cells (35), and in vivo studies of adrenal function in familial hypercholesterolemic and hypobetalipoproteinemic subjects (36–38, also see Ref. 18) are consistent with a potential role for HDL in human adrenocortical cholesterol metabolism.

We recently suggested that the type I class B scavenger receptor, SR-BI, is an attractive candidate receptor for cellular HDL-selective cholesteryl ester uptake (10). This receptor mediates HDL-selective cholesteryl ester uptake in transfected cells in culture and is prominently expressed in tissues which show high levels of HDL-selective uptake, such as the adrenal gland, ovary, and liver (3, 4, 8, 12). If SR-BI is a physiologically relevant receptor for HDL-selective cholesteryl uptake and provides substrate cholesterol for steroidogenesis, its expression should be subject to the same stimuli which alter selective cholesterol uptake activity and steroid hormone production (e.g. ACTH stimulation and glucocorticoid suppression of adrenocortical cells; Refs. 5, 19, and 20). Moreover, it should be specifically expressed in the hormone-producing cells of steroidogenic tissues.
In the present study, we have used immunoblotting and immunohistochemical methods to show that murine SR-BI (mSR-BI) is specifically expressed on the plasma membranes of steroid-producing adenocortical cells, and that its expression in vivo is induced by ACTH and suppressed by glucocorticoids. Thus, expression of SR-BI protein is coordinately regulated with adrenal steroidogenesis. These data provide strong support for the hypothesis that SR-BI is a physiologically relevant HDL receptor that provides substrate cholesterol for steroid hormone synthesis.

**EXPERIMENTAL PROCEDURES**

**Animals and Experimental Treatments—**Male and female C57BL/6J mice (2–4 months old) (Jackson Laboratories, Bar Harbor, ME) received standard mouse chow and water ad libitum and were maintained on a 12-h light/12-h dark cycle. Experiments were initiated 2 h into the light cycle. Mice received intraperitoneal injections of 0.1 ml of saline or 0.1 ml of saline containing either 4 units of ACTH (Acthar-gel, Rorer Pharmaceuticals, Fort Washington, PA), or 40 μg of dexamethasone phosphatate (Genica Pharmaceuticals) at time 0, 12 h, and 24 h. Three hours after the last injection, the mice were anesthetized with 0.05 ml of a mixture of ketamine (3 mg)/xylazine (0.4 mg), and tissues were removed and frozen for immunoblot analysis. For immunocytochemical studies, mice were perfused at constant pressure (110 mm Hg) through the left ventricle first with 0.1 ml of 0.1% sodium cacodylate, pH 7.4, followed by 25 ml of freshly prepared fixative A (4% paraformaldehyde in 0.1 M sodium cacodylate, pH 7.4). After overnight incubation in fixative A, isolated adrenal glands were embedded in paraplast x-tra. Immunoblotting and immunohistochemical analyses were performed on at least two mice (male, female, or both) in each experiment in four independent experiments.

**Cell Culture—**Murine Y1-BS1 adrenal cells were maintained in a 37 °C humidified 95% air, 5% CO2 incubator in medium A (Ham’s F-10 medium supplemented with 12.5% heat-inactivated horse serum and 2 mM glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin sulfate). For experiments, Y1-BS1 cells were plated in 150-mm dishes in medium A and cultured for 48 h until they were approximately 70% confluent. The cells were then refed with medium A containing no additions or ACTH and determined mSR-BI residues 495–509 (mSR-BI(495–509)) in 1% NGS in PBS or with preimmune antibody under identical conditions. Sections were then stained with Mayer’s hematoxylin.

**Immunoblotting of Adrenal Glands and Y1-BS1 Cells—**Whole adrenal gland homogenates were prepared as described previously (21). Subconfluent Y1-BS1 cells were washed and scrapped in PBS and lysed in 10 ml Tris-Cl, pH 7.3, 1 mm MgCl2, 0.5% Nonidet P-40, and 0.005% phenylmethylsulfonyl fluoride as described previously (22). Postnuclear supernatants from the adrenal gland homogenates and the Y1-BS1 cell lysates were prepared by centrifugation at 3000 × g for 10 min at 4 °C. Samples containing the indicated amounts of protein (23) were separated by 2.5% heat-inactivated fetal bovine serum with 2 mM glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin sulfate. For experiments, Y1-BS1 cells were plated in 150-mm dishes in medium A and cultured for 48 h until they were approximately 70% confluent. The cells were then refed with medium A containing no additions or ACTH (10−2 M) and, incubated overnight before harvesting for immunoblot analysis of SR-BI.

**Immunocytochemical Localization—**Adrenal sections (5 μm) were deparaffinized in xylene, rehydrated through graded ethanol solutions, and endogenous peroxidase activity was quenched with a 20-min immersion in 0.6% hydrogen peroxide in 80% methanol. Sections were blocked for 30 min in 10% normal goat serum (NGS) in phosphate buffered saline (PBS), incubated for 60 min with a rabbit antibody (3.6 μg/ml of purified IgG) directed against mSR-BI residues 495–509 (mSR-BI(495–509)) in 1% NGS in PBS or with preimmune antibody under identical conditions. Sections were then stained with Mayer’s hematoxylin.

**RESULTS**

Previous studies have shown that mSR-BI, an approximately 82-kDa glycoprotein, is expressed at high levels in the adrenal gland of untreated mice (10). To determine if mSR-BI expression is coordinately regulated with induced adrenal steroidogenesis, we injected mice with a saline solution with or without ACTH and determined mSR-BI protein levels using immunoblotting with an anti-mSR-BI antibody and a chemiluminescence detection system as described under “Experimental Procedures.” B, Y1-BS1 adrenal cells were plated on day 0 in 150-mm dishes in medium A. On day 2, the cells were refed with medium A containing no additions (lane 1) or 10−2 M ACTH (lane 2). After an overnight incubation, the cells were harvested, postnuclear supernatants were prepared, and the samples (20 μg of protein/lane) were subjected to immunoblot analysis as in A.

**Mass Standards** (Pharmacia Biotech Inc.) and to verify that the specimens were loaded and transferred with comparable efficiency.

**Fig. 1.** Immunoblot analysis of mSR-BI from adrenal glands in vivo (A) and Y1-BS1 adrenal cells in vitro (B): effects of hormone treatments. A, 2-month-old female mice were injected at times 0, 12 h, and 24 h, with normal saline (control, lanes 1 and 2) or saline containing either ACTH (4 units/animal, lanes 3 and 4) or dexamethasone phosphate (40 μg/animal, lanes 5 and 6). Three hours after the last injection, adrenal glands were harvested and mSR-BI protein in postnuclear supernatants from tissue homogenates (40 μg of protein/sample) was detected by immunoblotting with an anti-mSR-BI antibody and a chemiluminescence detection system as described under “Experimental Procedures.” B, Y1-BS1 adrenal cells were plated on day 0 in 150-mm dishes in medium A. On day 2, the cells were refed with medium A containing no additions (lane 1) or 10−2 M ACTH (lane 2). After an overnight incubation, the cells were harvested, postnuclear supernatants were prepared, and the samples (20 μg of protein/lane) were subjected to immunoblot analysis as in A.

**Immunoblotting of Adrenal Glands (in vivo)**

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immunoblotting to determine the effects of ACTH on mSR-BI levels in Y1-BS1 cells. Y1-BS1 is a murine adrenal cell line which exhibits ACTH-dependent selective cholesteryl ester uptake from HDL (24). Fig. 1B shows that mSR-BI expression was greatly increased in ACTH-treated cells compared to untreated control cells, indicating that adrenal mSR-BI expression is under direct, rather than indirect, control by ACTH.

To determine the cell type distribution of mSR-BI expression and the effect of ACTH and dexamethasone on this distribution, we performed immunohistochemical staining of murine adrenal gland sections taken from saline- or hormone-treated females. As shown in Fig. 2A, SR-BI immunostaining in the saline-treated control was seen in the adrenal cortex but not in the medulla. The locations of the cortical zones (Z. glomerulosa, Z. fasciculata, Z. reticularis, and X zone) were labeled as indicated, and arrowheads denote some of the sites at the cell surface where mSR-BI staining defines circular or oval structures. Bars represent 75 μm (A, C, and E) or 10 μm (B, D, and F).

**Fig. 2. Immunohistochemical localization of mSR-BI in adrenal glands of saline control, ACTH, and dexamethasone-treated mice.** Mice were injected with saline solution alone (control, A and B) or saline containing either ACTH (C and D) or dexamethasone (E and F) as described in the legend to Fig. 1. Their adrenal glands were isolated, embedded, sectioned, and stained with an anti-SR-BI antibody and a biotinylated goat anti-rabbit IgG/avidin-biotinylated peroxidase complex as described under “Experimental Procedures.” Representative fields were photographed at low (∼150, panels A, C, and E) or high (∼1200, panels B, D, and F) magnification. The medulla (M) and cortical zones (Z. glomerulosa (ZG), Z. fasciculata (ZF), Z. reticularis (ZR), and the X zone (X)) and sinusoids (s) in the Z. fasciculata are labeled as indicated, and arrowheads denote some of the sites at the cell surface where mSR-BI staining defines circular or oval structures. Bars represent 75 μm (A, C, and E) or 10 μm (B, D, and F).
seen only faintly within the degenerating X zone of this 2-month-old female mouse. The distribution of mSR-BI staining in males was similar to that in females (data not shown), although the X zone, a developmentally regulated zone of uncertain function, was absent in the 2-month-old males (25).

At higher magnification (×1200, Fig. 2B), immunostaining was most prominent on the plasma membrane of z. fasciculata cells both on the sinusoidal face as well as along intercellular junctions of parenchymal cells. mSR-BI stain often completely encircled the parenchymal cell. Little or no staining was seen over endothelial cell nuclei (data not shown) suggesting that sinusoidal staining reflects mSR-BI expression on the parenchymal cell surface. There was no significant staining of the tissues when the anti-mSR-BI antibody was replaced by pre-immune antibody (data not shown).

ACTH treatment markedly increased (Fig. 2, C and D) and dexamethasone treatment dramatically decreased (Fig. 2, E and F) immunostaining in the cortex (compare with Fig. 2, A and B). At higher magnification (×1200, Fig. 2D), intense staining in the ACTH-treated tissue was seen at both the sinusoidal surface and the intercellular junctions of z. fasciculata cells, confirming the presence of mSR-BI on all faces of the parenchymal cell. Interestingly, intense mSR-BI staining was often observed around small circles and ovals which lay along intercellular domains of plasma membrane as well as near junctions between cells on the sinusoidal surface (arrowheads in Fig. 2, B and D). The number of these intensely stained circles and ovals was far greater than can be appreciated when viewed at any one focal plane (Fig. 2). When we varied the microscope’s plane of focus (not shown), many more such structures could be seen, and the three-dimensional contiguity of the intense stain suggested that these features may represent cross-sections of intercellular canaliculi.

**DISCUSSION**

The mechanism of selective uptake of HDL cholesteryl ester by cells has remained elusive despite considerable effort over the past 15 years. SR-BI, which is a scavenger receptor that can bind a variety of macromolecules, including native and chemically modified LDL (26) and anionic phospholipids (27), was the first molecularly well-defined cell surface HDL receptor to be identified (10). Its ability to mediate selective cholesteryl ester uptake from HDL by cultured cells and its high level of expression in murine tissues which exhibit selective uptake in vivo (liver, nonplacental steroidogenic tissues) suggested that it may play a physiologically significant role in providing HDL cholesterol as substrate for cholesterol metabolism via selective uptake. Its ability to bind LDL (26) also raises the possibility that it might mediate transfer of LDL cholesterol to cells. In the liver, SR-BI might be involved in mediating the transport of HDL-cholesterol from peripheral tissues in the final stage of reverse cholesterol transport (13, 14).

In steroidogenic tissues, SR-BI is likely to be involved in providing cholesterol substrate for steroidogenesis. The present study provides strong support for this suggestion for the murine adrenal gland. HDL selective uptake is the predominant pathway for lipoprotein cholesteryl ester uptake in the rodent adrenal gland in vivo (3, 5), in cultured rat adrenocortical cells (4, 28), and in a murine Y1 adrenocortical cell line (20). This pathway is induced by ACTH (6, 19, 20) in concert with the increased production of corticosteroid that derives from HDL cholesteryl esters (28, 29). In the present study, immunohistochemical and immunoblotting studies established that mSR-BI is specifically expressed in steroidogenic cells of the adrenal gland and that in vivo ACTH administration dramatically increased mSR-BI protein expression, especially on the plasma membranes of these cells. In addition, administration of exogenous glucocorticoid, a treatment that suppresses endogenous ACTH levels and adrenocortical steroid production, dramatically suppressed mSR-BI protein expression by adrenocortical cells. Thus, there is a strong correlation in the adrenal gland of the induction by ACTH of the HDL cholesteryl ester selective uptake pathway, the utilization of this cholesterol for steroid production, and the induction of SR-BI protein expression. In addition, it seems likely that ACTH stimulated adrenal gland mSR-BI expression by interacting directly with adrenocortical cells, rather than indirectly through stimulation of other types of cells, because we observed ACTH stimulation of mSR-BI expression in cultured Y1-B51 adrenal cells. Others have previously shown ACTH-inducible selective cholesterol uptake from HDL by Y1-B51 cells (24), and we have confirmed these observations under conditions identical to those used to examine SR-BI expression (not shown). Additional studies will be required to define the mechanism underlying ACTH induction of SR-BI protein expression and the associated increase in cholesterol uptake. Taken together, these data strongly support the hypothesis that mSR-BI mediates selective uptake of HDL cholesteryl esters which in turn serve as substrate for corticosteroid synthesis in adrenocortical cells. It is possible that induction of SR-BI expression in adrenal cortical cells may also increase cholesterol delivery from LDL, because LDL is a high affinity ligand for SR-BI (26). Indeed, LDL receptors in adrenal cortical cells are induced by ACTH (29, 39). However, there is much less LDL than HDL in the plasma of mice (40), and a significant fraction of this LDL contains apoB48 that cannot bind to LDL receptors. Furthermore, we have previously reported that LDL is a very poor competitive inhibitor of HDL binding to SR-BI expressed in cultured cells (10). Thus, while the significance of LDL binding by SR-BI remains to be explored, this binding is unlikely to interfere with the in vivo association of HDL with SR-BI.

Our hypothesis that SR-BI mediates selective uptake of HDL cholesteryl esters in vivo is also supported by our recent complementary studies of hormonal regulation of SR-BI expression in the rat (30). High dose, prolonged estrogen treatment was shown to induce SR-BI expression in steroidogenic cells of the ovary (e.g. corpus luteal cells) and adrenal gland (cortical cells) of rats and reduce SR-BI in the liver. In addition, administration of human chorionic gonadotropin, which stimulates testosterone production in Leydig cells in the testes, dramatically increased SR-BI expression specifically in Leydig cells. The regulated levels of SR-BI protein expression in these tissues was correlated with fluorescent lipid uptake from HDL. Thus, in both mice and rats we have observed a striking correlation of both hormonal induction of steroidogenesis and selective cholesterol uptake from HDL with induction of SR-BI protein expression. Indeed, the current studies, which establish that ACTH regulates adrenal gland SR-BI expression in vivo, suggest an explanation for the induction of rat adrenal gland SR-BI by estrogen. Burgess and colleagues (31, 32) have reported that, in rats, chronic estrogen treatment interferes with glucocorticoid receptor-mediated slow negative feedback, which can result in increased and prolonged levels of plasma ACTH and corticosterone after stress. Thus, in the rat, induction of adrenal gland SR-BI expression by estrogen may be an indirect consequence of estrogen-induced increases in ACTH production due either to suppression of feedback or to the substantial stress associated with the consequences of chronic high dose estrogen administration, or both. This conclusion is supported by the observation of a dramatic decrease in immunodetectable SR-BI in the adrenal gland of hypophysectomized rats (30).

Selective uptake of cholesteryl esters from HDL is believed to
occur in specialized HDL-filled microvillar channels that are formed by juxtaposition of adjacent microvilli on parenchymal cells of the adrenal cortex (33). Microvilli and microvillar channels are abundant in the subendothelial space adjacent to the sinusoid (33) as well as in intercellular canaliculi that occur along the junctions of adjacent z. fasciculata cells (25, 34). In the rat, canalicular microvilli, as well as subendothelial microvilli, show immunoreactivity for apoA-I indicating the presence of HDL particles in these adenocortical canaliculi (34). At the light microscopic level, apoA-I (detected by immunostaining) surrounds the cell, suggesting that selective uptake from HDL occurs on all faces of the parenchymal cell (34). In the present study, immunostain for mSR-BI exhibited a nearly identical distribution as previously reported for apoA-I, including the encirclement of the parenchymal cell. Interestingly, intense mSR-BI immunostaining was seen along the intercellular junctions of z. fasciculata cells in numerous circular and oval structures that may represent the intercellular canaliculi noted above. The localization of mSR-BI to these regions provides further support for the proposal that mSR-BI mediates the selective uptake of HDL cholesteryl ester in vivo.

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Note Added in Proof—While this work was under review, Wang et al. (41) reported the analysis of the expression of SR-BI in various strains of mutant mice and in cultured Y1 adrenal cells.

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