

# Scavenger receptor class B type I expression in murine brain and regulation by estrogen and dietary cholesterol

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## Abstract

The scavenger receptor class B type I (SR-BI), a receptor for high-density lipoproteins (HDL), facilitates cholesterol delivery to steroidogenic tissues, and brings excess body cholesterol to liver for excretion. Scavenger receptors are also involved in the internalization of aggregates of Alzheimer's disease (AD) amyloid  $\beta$ -protein, and selective uptake of HDL-associated vitamin E in the brain. Therefore, modulation of the brain SR-BI may affect these processes. The present study examined the expression of SR-BI receptors in murine brain and their regulation by estradiol administration and cholesterol feeding. Liver and brain appeared to express similar SR-BI transcripts. Expression of SR-BI was highest in the adrenals and lowest in the brain. In rats, estradiol administration decreased SR-BI in liver, but increased in adrenals. In mice, estrogen treatment decreased hepatic SR-BI, but interestingly increased the levels of brain SR-BI mRNA. Cholesterol feeding did not alter mouse hepatic SR-BI mRNA, but increased brain SR-BI levels. ATP-binding cassette transporter A1 (ABCA1), involved in cellular cholesterol transport, increased in cholesterol-fed mouse liver, but did not show changes in the brain. These studies suggest that SR-BI is expressed in the brain and regulated by hormonal and nutritional stimuli, which may influence the pathophysiology of neurological disorders like AD.

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**Keywords:** Scavenger receptors; Alzheimer's disease; Estrogen; Cholesterol; Mouse; Brain; ABCA1; Real-time PCR; RNase protection assay

## 1. Introduction

Scavenger receptor class B type I (SR-BI) is a physiological high-density lipoprotein (HDL) receptor [1,2] that facilitates the selective uptake of HDL cholesteryl esters (CE) by the liver in a process called reverse cholesterol transport. The selective uptake of HDL-CE by liver parenchymal cells is efficiently coupled to bile acid synthesis and secretion [3]. This process differs fundamentally from the LDL receptor-mediated uptake of lipoproteins in that HDL particles are not taken up as holoparticle like in LDL receptor-mediated pathway [4]. Since SR-BI is involved in

the reverse cholesterol transport that removes excess cholesterol from the body, the modulation of SR-BI by physiological, pharmacological, and nutritional stimuli may also affect the HDL-mediated reverse cholesterol transport. In addition to binding to HDL particles, SR-BI also binds to the native LDL, modified LDL and anionic phospholipids [5,6], and can mediate selective uptake of oxidized cholesterol esters by rat hepatocytes [7]. SR-BI influences the efflux of cholesterol from the cells [8], and SR-BI receptors are expressed at highest levels in the steroidogenic tissues that require continuous supply of cholesterol to be used as a precursor for the synthesis of steroid hormones [9]. Overexpression of hepatic SR-BI in mice lowers plasma levels of HDL and increases biliary cholesterol [10], and disruption of the mouse SR-BI gene results into increased levels of plasma cholesterol [11], suggesting the important role of SR-BI in cholesterol transport. Estrogens modulate the hepatic and adrenal SR-BI receptors in rats [12] and in induced mutant mice lacking apolipoprotein A1 (apoA1) or hepatic lipase [13]. SR-BI is expressed in a variety of tissues as determined by Northern blotting analysis [9,12]. Although SR-BI-specific band was not visible on the brain

*Abbreviations:* SR-BI, scavenger receptor class B type I; ABCA1, ATP-binding cassette transporter A1; DEPC, diethyl pyrocarbonate; CE, cholesteryl ester; ApoA1, apolipoprotein A1; RT-PCR, reverse transcription-polymerase chain reaction; AD, Alzheimer's disease; SREBP, sterol responsive element binding protein.

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RNA blots of rat and mouse [9,12], recent studies suggested the expression of SR-BI in the rat brain [14,15] and in porcine brain capillary endothelial cells [16]. SR-BI expression was also reported in the human brain [17,18]. Involvement of scavenger receptors in the internalization of amyloid beta protein by microglial cells has been suggested [19,20]. However, a detailed study on the expression and regulation of brain SR-BI has not been carried out. This report describes the cloning of part of the mouse brain SR-BI and regulation of its expression by estradiol administration and cholesterol feeding.

## 2. Materials and methods

### 2.1. Animals and treatments

Rats and mice were administered 17  $\beta$ -estradiol as described in Ref. [21]. Male Sprague–Dawley rats weighing 200–250 g were purchased from Harland Sprague–Dawley (Indianapolis, IN). One group of rats ( $n=3$ ), placebo group, was administered 1.6  $\mu$ l propylene glycol/g body weight daily. The treatment group received 5  $\mu$ g/g body weight/day, 17  $\beta$ -estradiol dissolved in propylene glycol. The treatment was performed for 6 days. Rats had free access to rodent chow diet and tap water. Male C57BL mice, obtained from Jackson Laboratories, Bar Harbor, ME, were treated in a

similar way. Rats and mice were sacrificed on the seventh day under pentobarbital anesthesia. Plasma was used for the analysis of lipoproteins, and organs were excised for the preparation of RNA and membrane fractions.

Groups of female C57BL mice were fed either chow diet or diet containing 0.5% cholesterol and 20% hydrogenated coconut oil as described in Refs. [22,23]. At the end of the 3 weeks feeding, mice were sacrificed using phentobarbital. Plasma was analyzed for lipoprotein profiles, and organs were removed for the preparation of RNA and membrane fractions.

### 2.2. Partial cloning of the mouse brain SR-BI

One microgram of the total RNA isolated from mouse liver and brain was taken for reverse transcription-polymerase chain reaction (RT-PCR). Following primer pair was used for the reverse transcription-polymerase chain reaction:

5' primer-TTTCAGCAGGATCCATCTGGTGGGA (731–754 nt)  
3' primer-AGTTCATGGGGATCCCAGTGAC (1200–1177 nt)

These primers were designed from the published sequences of mouse SR-BI cDNA obtained from the Gene Bank. One microgram total RNA was reverse transcribed using 2

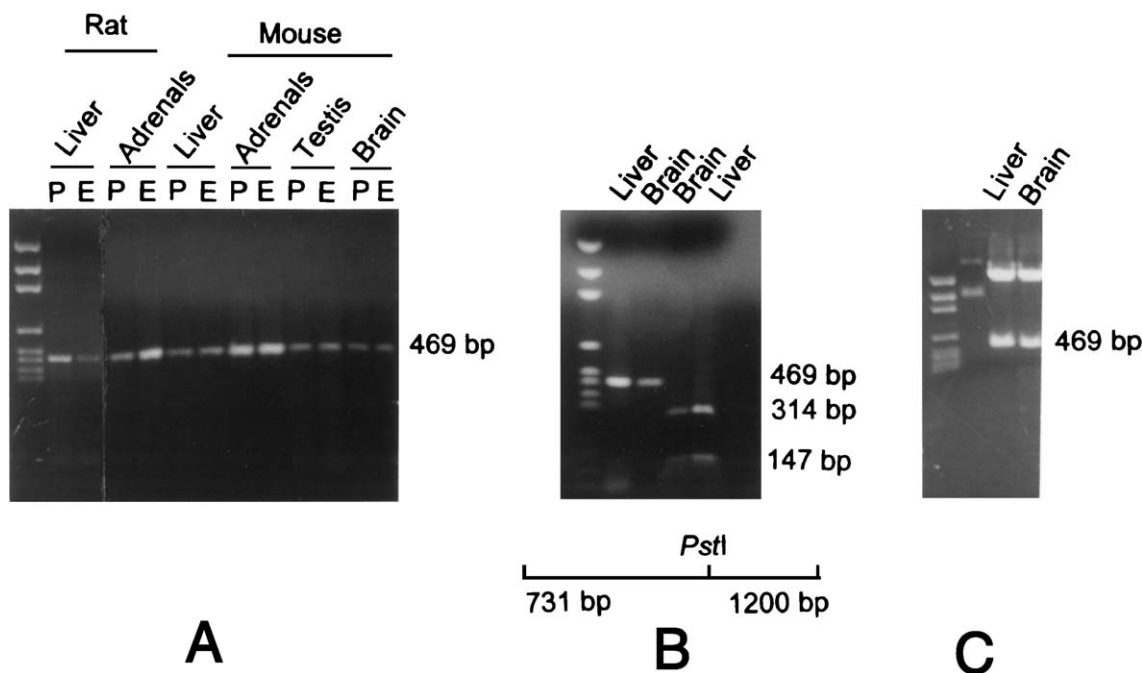


Fig. 1. Panel A, RT-PCR of rat and mouse SR-BI. One microgram of total RNA prepared from various tissues was reverse transcribed using a 3' primer described in Materials and methods, and the resulting cDNA was amplified by a pair of 5' and 3' SR-BI primers derived from mouse SR-BI cDNA sequence obtained from Gene Bank. Panel A shows RT-PCR products of RNA samples from placebo-treated (P) or 17  $\beta$ -estradiol-administered (E) rat or mouse as indicated. Panel B, the RT-PCR product obtained with mouse liver and brain RNA samples were restriction digested with *Pst*I and the resulting digests were resolved in 1% agarose gel. Lane 1, DNA size markers; lane 2, uncut RT-PCR products obtained with liver RNA; lane 3, uncut RT-PCR product obtained with brain RNA; lanes 4 and 5, RT-PCR products restriction digested with *Pst*I. Panel C, the RT-PCR products obtained with liver and brain RNA samples were subcloned into PGEMT vector (Promega), and recombinant plasmids prepared were checked by restriction digestion with restriction endonuclease *Eco*RI.

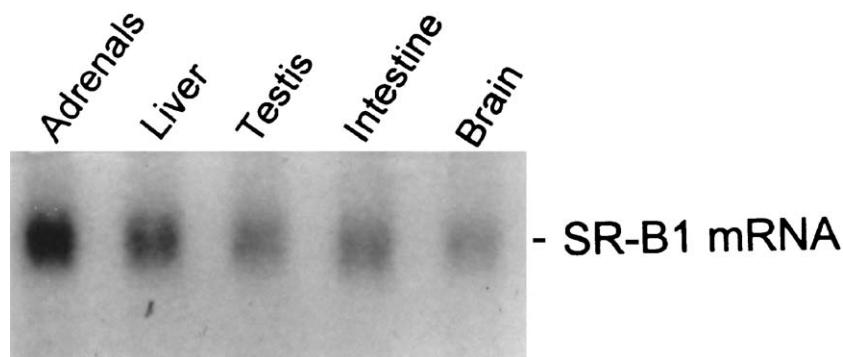


Fig. 2. Expression of SR-BI mRNA in various mouse tissues. Fifteen micrograms of total RNA from various tissues (30  $\mu$ g from brain) was electrophoresed in 1.2% agarose gel containing formaldehyde and formamide, transferred onto a nylon membrane, and probed with mouse SR-BI riboprobe synthesized in vitro.

$\mu$ l of the above primer pairs (20  $\mu$ M) in a total volume of 50  $\mu$ l using Titan one tube RT-PCR system obtained from Boehringer Mannheim-Life technology and following the protocol provided by the supplier of the RT-PCR system. Following profile was used to obtain RT-PCR product. One cycle: 50  $^{\circ}$ C, 50 min; one cycle: 94  $^{\circ}$ C, 2 min; 30 cycles: 94  $^{\circ}$ C, 30 s, 58  $^{\circ}$ C, 30 s, 68  $^{\circ}$ C, 1 min; one cycle: 72  $^{\circ}$ C, 7 min. The RT-PCR product was analyzed in 1% agarose gel and purified using PCR purification kit obtained from Qiagen. The purified PCR product was checked on 1% agarose gel and used for subcloning into the pGEM-TEASY plasmid obtained from Promega. The subcloned SR-BI cDNA fragment was checked by restriction digestion as well as by dideoxy DNA sequencing. The recombinant clone with the mouse SR-BI cDNA and the linearized recombinant plasmid for riboprobe synthesis were obtained from CloneGen Biotechnology, Ann Arbor, MI.

### 2.3. Isolation and analysis of SR-BI mRNA

Total RNA from various tissues was prepared by one-step RNA-isolation procedure as described before in Ref. [24]. SR-BI mRNA was quantitated using Northern blot, and RNase protection assay using the reagents and the recombinant clone procured from CloneGen as described in Refs. [25,26]. For Northern blotting analysis, 15  $\mu$ g total RNA was electrophoresed in 1.2% agarose gel containing formaldehyde and formamide. After the electrophoresis, the RNA from the gel was transferred onto a nylon membrane (Nytran) and fixed by baking at 80  $^{\circ}$ C in an oven for 1 h. The membrane was probed using  $\alpha^{32}$ P-labeled mouse SR-BI cDNA probe cloned as described.

To measure SR-BI mRNA levels in various tissues using RT-PCR, 1  $\mu$ g total RNA was reverse transcribed and amplified by polymerase chain reaction as described above, and 5  $\mu$ l product was analyzed in a 1% agarose gel. For the RNase protection assay, the 469-bp-cloned SR-BI fragment in pGEMT vector was linearized using *Nco*I restriction endonuclease, and the resulting linearized recombinant plasmid was purified by phenol chloroform extraction followed by ethanol precipitation. The precipitate was washed with

70% ethanol and dissolved in appropriate amounts of diethyl pyrocarbonate (DEPC)-treated water. One microliter of the linearized plasmid was examined on the agarose gel to check the concentration and the completion of linearization. The linearized plasmid was used for the in vitro transcription using in vitro transcription kit obtained from CloneGen, in the presence of T7 RNA polymerase  $\alpha$ - $^{32}$ P-CTP, UTP, ATP, and GTP, DTT, transcription buffer, and RNase inhibitor as described in Ref. [27]. After the transcription, the linearized recombinant plasmid DNA was digested with RNase-free DNase I, and the resulting reaction mixture was purified using Sephadex G-50 column. The label incorporation into the transcribed riboprobe was checked by counting 2  $\mu$ l of the 1:10 dilution of the riboprobe in a liquid scintillation counter. As an internal control,  $\beta$ -actin riboprobe was synthesized in a

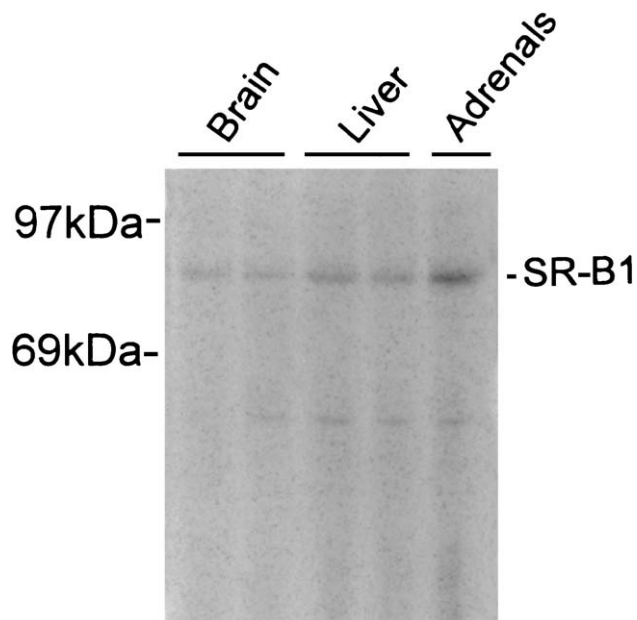


Fig. 3. Measurement of SR-BI protein in various mouse tissues. Membrane fractions were solubilized and 60  $\mu$ g protein (100  $\mu$ g for brain) was separated in 7% SDS-polyacrylamide gels, transferred onto PVDF membrane, and probed with polyclonal rabbit antipeptide antibody raised against the last 14 amino acids of mouse SR-BI.

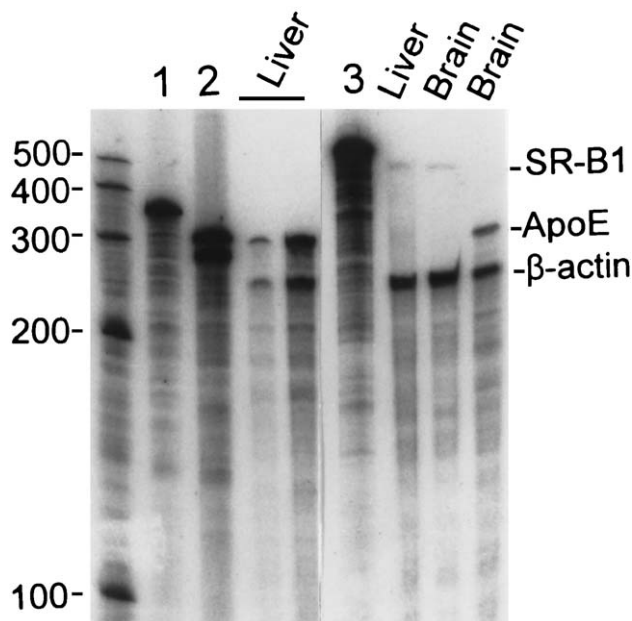


Fig. 4. RNase protection assay of SR-BI. RNase protection assay for SR-BI was set up using mouse hepatic and brain RNA samples. Since mouse brain expresses highest levels of apoE next only to the liver, apoE was also measured as a control in the same brain RNA sample. Beta actin was used as an internal control. Recombinant SR-BI plasmid was linearized with *NcoI* and in vitro transcription performed using SP6 RNA polymerase as described in Ref. [18]. Recombinant apoE plasmid was linearized with *PstI* and T7 RNA polymerase was used to transcribe riboprobe in the presence of ribonucleotides ATP, TTP, GTP, and  $\alpha$ - $^{32}$ P-labeled CTP. The leftmost lane shows in vitro transcribed RNA markers. Lane 1, apoE riboprobe; lane 2, beta-actin riboprobe; lane 3, SR-BI riboprobe; next to lane 2 are two lanes showing apoE and  $\beta$ -actin hybridization with 5 and 20  $\mu$ g total liver RNA, and next to lane 3 are three lanes showing protection assay for SR-BI and apoE as a control.

similar way. The riboprobes were either used immediately or stored at  $-80^{\circ}\text{C}$  and used within 2 weeks. RNase protection assay was carried out using RPAHyb kit obtained from CloneGen and following the protocol provided by the manufacturer. Thirty microgram total RNA was dried in a Speed Vac followed by the addition of 2  $\mu$ l of riboprobe (150,000 cpm). Fifteen microliter of prewarmed ( $95^{\circ}\text{C}$ ) RPAHyb buffer (CloneGen) was added and vortexed for 20 s followed by incubation at  $65^{\circ}\text{C}$  for 4 h. One hundred microliter of RNase A/T1 buffer (1:50 dilution) was then added and incubated for 30 min at  $37^{\circ}\text{C}$  followed by the addition of 150  $\mu$ l of inactivation/precipitation buffer. This mixture was incubated at  $-20^{\circ}\text{C}$  for 30 min and spun at 12,000 rpm for 10 min in a tabletop centrifuge. The supernatant was discarded. The pellet was dissolved in 10  $\mu$ l of loading buffer, heated for 3 min at  $90^{\circ}\text{C}$ , and loaded in a 6% sequencing gel. After the electrophoresis, the sequencing gel was dried carefully and exposed to X-ray film. The intensities of the respective mRNA bands were determined by densitometry.

Hepatic and brain RNA samples were also analyzed for SR-BI and ATP-binding cassette transporter A1 (ABCA1) mRNA using TaqMan (Applied Biosystems) real-time PCR.

Sixty nanogram of total RNA was reverse transcribed and amplified using probe and primer pairs, designed using the Primerexpress software obtained from Applied Biosystems. As an internal control, 18S RNA was also quantitated in the same tube. Each RNA sample was analyzed in triplicate.

#### 2.4. Analysis of SR-BI protein

To measure the SR-BI protein, membranes were prepared from various tissues as described in Ref. [12]. Membrane preparations were separated on a 7% SDS-polyacrylamide gel electrophoresis, transferred onto PVDF membrane, and detected with polyclonal anti-SR-BI antibody raised in rabbit against the C-terminal 14 amino acids of the mouse SR-BI.

### 3. Results

As determined by a semiquantitative RT-PCR method, estrogen administration decreased SR-BI mRNA in rat liver,

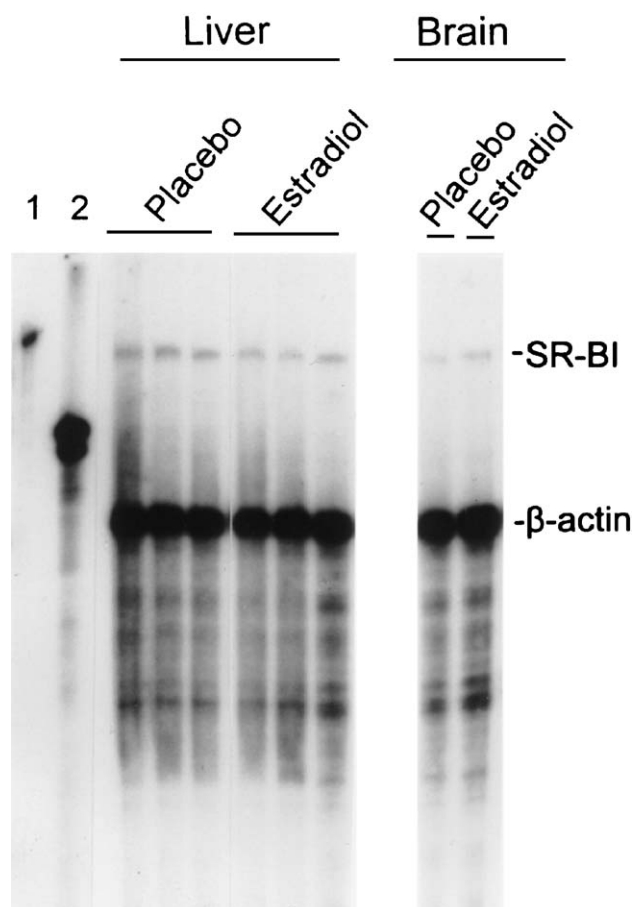


Fig. 5. Quantitation of SR-BI in the liver and brain RNA from placebo- and estradiol-treated mouse. Fifteen micrograms of total RNA was taken for the protection assays. Lane 1, SR-BI riboprobe; Lane 2, beta actin riboprobe. RNA from three individual mouse livers was taken for protection assay. For the analysis of brain SR-BI, pooled RNA from three individual mouse brain was taken for the protection assay.

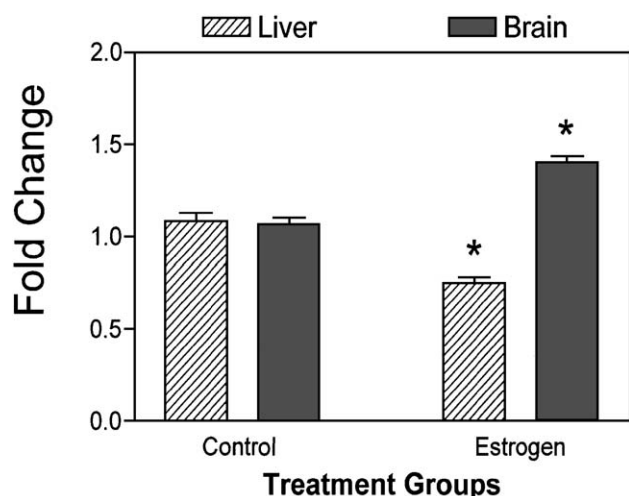


Fig. 6. Quantitation of SR-BI mRNA in the liver and the brain RNA from placebo- and estradiol-treated mice using TaqMan real-time PCR. 18S RNA was taken as an internal control in the same tube. The probe and the primers were designed using PrimerExpress software (Applied Biosystem). Sixty nanograms of total RNA from individual RNA preparation ( $n=3$ ) was taken in triplicate for real-time PCR. So, each bar represents nine measurements. In order to see the variability, the quantitative PCR was performed at least two times. The striped bars represent liver and the filled bars represent brain. \*Significantly different from the placebo group.

while SR-BI mRNA increased in the rat adrenals (Fig. 1A). In an earlier study [12], immunoblot showed a prominent SR-BI protein band in the rat liver, but this protein band almost disappeared following estrogen treatments, suggesting a potent effect of estrogen on the regulation of the rat hepatic SR-BI protein. Whether or not this lowering of SR-BI protein was due to transcriptional or posttranscriptional mechanisms was not demonstrated. Using a semiquantitative RT-PCR method, it is shown that estrogen lowers rat hepatic SR-BI and elevates adrenal SR-BI by modulating the levels of SR-BI mRNA, which could occur either by a transcriptional or posttranscriptional mechanism. In mouse, estrogen administration did not appear to alter SR-BI mRNA in the liver, adrenals, and the brain (Fig. 1A). The RT-PCR products obtained from the liver and the brain were verified by restriction digestion with *Pst*I, which gave the desired products and suggested that liver and brain SR-BI transcripts had the same restriction endonuclease site (Fig. 1B). Subcloning of the SR-BI cDNA fragment in pGEM-TEASY vector (Fig. 1C) and DNA sequencing further confirmed that the amplified sequences were of SR-BI transcript both in the liver and in the brain. Alignment of the sequences of these amplified fragments showed an exact match between the SR-BI cDNA fragment isolated from the liver and the brain. Using this cloned SR-BI cDNA (469 bp) as a probe for Northern blotting analysis, it was found that SR-BI mRNA was expressed at highest levels in the adrenals followed by the liver. Since SR-BI mRNA signal was not present in the RNA blot analysis in an earlier study [12], the amounts of RNA taken in the lane denoted as brain

were doubled compared to adrenals and liver (Fig. 2). The presence of an SR-BI-specific band on the Northern blot suggested the expression of SR-BI in the brain. To further confirm that indeed SR-BI is expressed in the brain, immunoblotting of the membrane proteins was carried out. Again, the amounts of protein taken for the analysis of the brain samples were twice the amount taken from the liver or adrenal tissue samples. It is evident that the SR-BI protein is expressed in the brain (Fig. 3). To precisely quantitate SR-BI mRNA in the liver and the brain, RNase protection assay was performed. The specificities of the riboprobe for SR-BI,

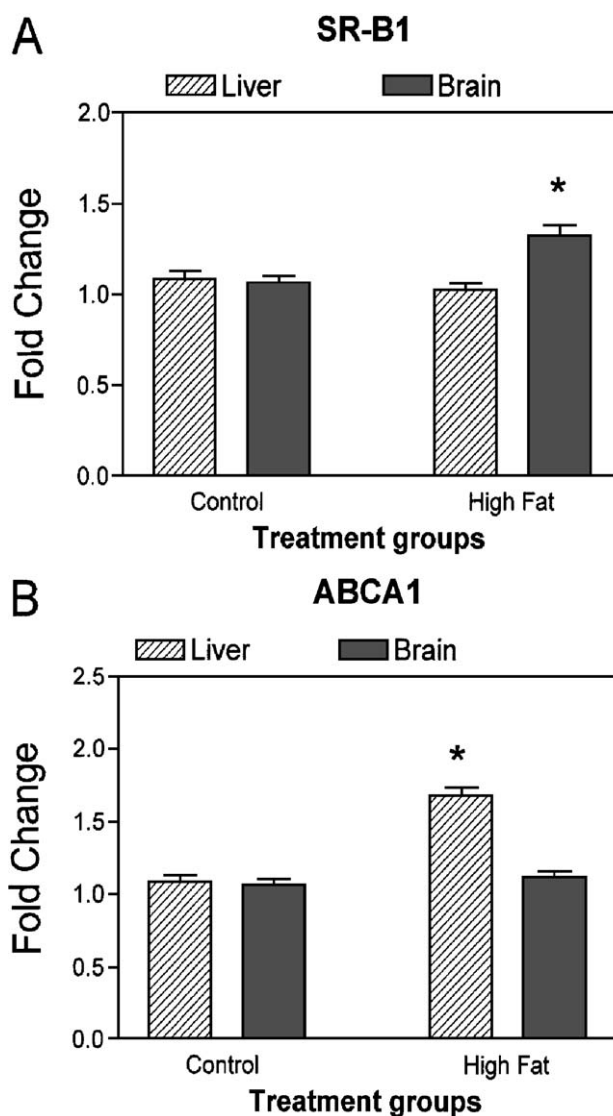


Fig. 7. Panel A, quantitation of SR-BI mRNA in the liver and the brain RNA samples from mice fed high-cholesterol, high-fat diet. RNA from the individual mouse ( $n=3$ ) was analyzed in triplicate for SR-BI mRNA using TaqMan real-time PCR as described in Fig. 6. Panel B, quantitation of ABCA1 mRNA in the liver and brain RNA samples in mice fed high-cholesterol, high-fat diet. RNA from three mice was analyzed individually in triplicate. The striped bars represent liver, and filled bars represent brain. \*Significantly different compared to control.

and another protein expressed abundantly in the liver, apoE, were determined to validate the assay. As shown in Fig. 4, protected riboprobe fragments corresponding to apoE and SR-BI were observed on the sequencing gel. Using the SR-BI riboprobe, RNase protection assay was performed on the individual liver samples from three mice in each group, and pooled brain RNA samples from three mice in each group. As shown in Fig. 5, estrogen treatment decreased SR-BI mRNA in the mouse liver, while brain SR-BI mRNA increased following estrogen treatment. To further confirm that estrogen treatment decreased liver SR-BI mRNA and increased brain SR-BI mRNA, TaqMan real-time RT-PCR was performed. As shown in Fig. 6, the TaqMan quantitative PCR corroborated the results obtained by RNase protection assay [5]. The semiquantitative RT-PCR shown in Fig. 1A could not detect small changes in the levels of brain SR-BI mRNA.

Regulation of the hepatic and the brain SR-BI was also examined in mice fed high-cholesterol and high-fat diet. These diets did not contain cholic acid. The RNA prepared from liver and brain tissues was analyzed by quantitative real-time PCR, and the results are shown in Fig. 7A. As shown, the high-fat diet did not appear to alter hepatic levels of SR-BI, while brain SR-BI expression increased following high-cholesterol, high-fat diet feeding (Fig. 7A). Another protein, ABCA1, expressed in the brain and involved in cholesterol trafficking, was quantitated by quantitative real-time PCR showed that high-fat feeding increased the hepatic expression of ABCA1, but did not alter brain expression of ABCA1 (Fig. 7B).

#### 4. Discussion

The aim of the present study was to demonstrate the expression of SR-BI in murine brain by cloning part of the brain SR-BI, compare the sequences with the same segment of cDNA obtained from the liver, and investigate the regulation by estradiol administration and dietary fat feeding. The sequences of the cloned SR-BI cDNA from the murine brain (469 bp corresponding to nucleotides 731–1177) matched completely with the hepatic SR-BI cDNA sequences, suggesting that similar SR-BI transcripts are expressed in the brain and the liver. The RT-PCR method was able to detect low levels of SR-BI expression in the brain RNA samples. Despite RT-PCR being semiquantitative, it was evident that estradiol administration lowered SR-BI transcripts in the liver and increased in the adrenals, consistent with an earlier report [12]. However, the potential mechanism of this dramatic lowering of hepatic SR-BI protein remained to be demonstrated. Here, it is shown that the lowering of the hepatic SR-BI by estrogen resulted from changes in the levels of SR-BI mRNA either by transcriptional or posttranscriptional mechanism. It is possible that estrogen's effect on SR-BI mRNA occurred via the interaction with estrogen response element in the SR-BI pro-

moter [28]. In mice, estradiol administration did not show any detectable differences in the levels of SR-BI transcripts in liver, adrenals, testes, and brain when compared to control group. This is an important finding, since rats and mice also show dramatic differences in the regulation of the hepatic LDL receptor [21]. While estradiol administration caused upregulation of the hepatic LDL receptors in the rat, it did not alter mouse hepatic LDL receptor [21]. Thus, rat and mouse differ in the responsiveness to estradiol administration.

That mouse brain expresses SR-BI was further confirmed by Northern blotting analysis, which was also corroborated by the levels of SR-BI protein expression in the brain. Consistent with the earlier studies, highest levels of SR-BI were expressed in the adrenals followed by the liver. The expression level of SR-BI in the brain was very low compared to the adrenals and the liver.

Estradiol treatment decreased SR-BI in mouse liver (Figs. 5 and 6), but the decreases were not as dramatic as in the estradiol-treated rats [12]. A major finding of the present study is the upregulation of the brain SR-BI in estradiol-administered mice. This finding is important, since SR-BI may be involved in the transport of HDL particles for the delivery of lipid-soluble vitamins to the brain [16]. A recent *in vitro* study in porcine brain capillary endothelial cells suggests that brain expression of SR-BI is involved in the cholesterol efflux [29]. The upregulation of SR-BI by estradiol may enhance the transport of lipid-soluble vitamins to the brain and protect from the oxidative stress-induced damage of brain cells observed in neurodegenerative disorders. Since ABCA1 is involved in the cellular cholesterol transport, and recently in the uptake of vitamin E [30], ABCA1 mRNA in the liver and the brain RNA samples of the estradiol-treated mice was also quantitated. Liver expressed three times higher levels of ABCA1 transcripts compared to brain. Estradiol treatment increased hepatic ABCA1 expression, but did not alter brain ABCA1 transcripts (Fig. 7B). It therefore appears that hepatic SR-BI and ABCA1 are regulated by estradiol in the opposite direction.

Regulation of SR-BI expression was also studied in the liver and the brain of high-cholesterol- and high-fat-fed mice. Although high-fat feeding did not influence hepatic SR-BI expression, it increased the levels of brain SR-BI mRNA, suggesting that the brain SR-BI expression is regulated by nutritional stimuli. Feeding high-cholesterol diet to wild-type mice did not alter hepatic SR-BI protein [31]. The results reported here suggest that no changes in the hepatic SR-BI levels possibly occurred as a result of unaltered transcription of the SR-BI. In the present study, mice were fed saturated fat in the form of hydrogenated coconut oil together with 0.5% cholesterol, while in the other study [31], mice were fed either cholesterol alone (2%) or cholesterol/fat/cholic acid (1.25% cholesterol, 15% fat, 0.5 cholic acid) diet. None of these diets affected hepatic SR-BI protein. In hamsters,

polyunsaturated fatty acids (PUFA) increased the hepatic SR-BI mRNA and protein [32], but hydrogenated coconut oil did not affect either the SR-BI protein or the mRNA levels, similar to the results reported here in mice fed cholesterol and hydrogenated coconut oil. ABCA1 mRNA was quantitated in the liver and the brain RNA samples of high-fat-fed mice. Interestingly, hepatic ABCA1 mRNA showed significantly higher levels, while brain ABCA1 did not show any changes, suggesting that SR-BI and ABCA1 gene expressions are regulated independently, and under certain conditions, in the opposite direction. In the macrophages, mono- and polyunsaturated fatty acids lowered ABCA1 [33]. Since PUFA also downregulates lipogenic enzymes via the sterol responsive element binding protein (SREBP) 1- and 2-mediated pathways [34,35], this can lower cellular cholesterol levels and modulate ABCA1 expression. Therefore, one would expect ABCA1 to be downregulated and SR-BI to be upregulated by PUFA. In hamsters, PUFA upregulates SR-BI, but it is not known whether or not PUFA regulates ABCA1 *in vivo*. SR-BI and ABCA1 are involved in the cellular cholesterol efflux, but their mechanism of cholesterol transport across the cell membrane appears to be different. Whereas SR-BI is capable of bidirectional flux of cholesterol, ABCA1 mediates unidirectional flux of cholesterol. Roles of SR-BI and ABCA1 in cholesterol efflux in macrophages were carried out in cells transfected with SR-BI or treated with cAMP to upregulate ABCA1 [36]. The overexpression of SR-BI inhibited ABCA1-mediated cholesterol efflux in macrophages. One caveat of this study is that they were done in nonpolarized macrophages, therefore, these results are unlikely to be extrapolated to liver cells where SR-BI and ABCA1 are expressed on the different sides of the cell. Nevertheless, despite SR-BI and ABCA1 sharing common functions of cholesterol efflux, they are regulated differently by hormonal and nutritional stimuli in a tissue-specific manner. Existing data suggest that under certain physiological or pharmacological conditions, SR-BI and ABCA1 may be regulated differently, or in the opposite direction.

In summary, it is shown that similar SR-BI transcripts are expressed in the liver and the brain, and hormonal and nutritional stimuli regulate SR-BI expression in a tissue-specific manner. The expression and the regulation of brain SR-BI by estradiol and high-fat diet may have important implications in the pathogenesis of neurological disorders like AD and also in the local cholesterol transport in the brain.

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