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Immunohistochemical Localization of Type 1 11β-Hydroxysteroid Dehydrogenase in Human Tissues*

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ABSTRACT

Two isozymes of 11β-hydroxysteroid dehydrogenase (11βHSD) catalyze the interconversion of hormonally active cortisol to inactive cortisone. Activity and messenger ribonucleic acid studies indicate that type 1 11βHSD (11βHSD1) is expressed in glucocorticoid target tissues such as liver, gonad, and cerebellum, where it regulates the exposure of cortisol to glucocorticoid receptors. To further understand the role of 11βHSD1 in human tissues, we have studied the localization of this isozyme using an antibody raised in sheep against amino acids 19–33 of human 11βHSD1. Western blot analyses indicated that the immunopurified antibody recognized a band of approximately 34 kDa in human liver and decidua. Immunoperoxidase studies on liver, adrenal, ovary, decidua, and adipose tissue indicated positive cytoplasmic staining for 11βHSD1. 11βHSD1 immunoreactivity was observed more intensely around the hepatic central vein, with no staining around the portal vein, hepatic artery, or bile ducts. No staining for 11βHSD1 was observed in the adrenal medulla, but 11βHSD1-immunoreactive protein was observed in all three zones of the adrenal cortex, with the most intense staining in the zona reticularis > zona glomerulosa > zona fasciculata. In the human ovary, immunoreactivity was observed in the developing oocyte and the luteinized granulosa cells of the corpus luteum. No staining was observed in granulosa cells, thecal cells, or ovarian stroma, which contrasted with the marked expression of 11βHSD2 in the granulosa cell layer. Sections of human decidua showed high expression of 11βHSD1 in decidual cells. In omental adipose tissue, 11βHSD1 immunoreactivity was observed in both stromal and adipocyte cells. Immunohistochemical localization of 11βHSD1 in human liver, adrenal, ovary, decidua, and adipose tissue using this novel antiserum provides us with a tool to investigate the role of this isozyme in modulating glucocorticoid hormone action within these tissues. (*J Clin Endocrinol Metab* **83:** 1325–1335, 1998)

IN MAN, two distinct isozymes of the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) catalyze the interconversion of hormonally active cortisol (Kendall's compound F) to the inactive 11-keto metabolite cortisone (compound E) (1, 2). The type 1 isozyme of 11βHSD (11βHSD1) is a low affinity NADP/NADPH-dependent dehydrogenase/oxo-reductase, with an apparent K_m for F of 2.1 μmol/L, and for E of 0.3 μmol/L (3). In keeping with these kinetic data, the predominant role of this isozyme *in vivo* has been shown to be 11-oxo-reduction, *i.e.* the generation of active glucocorticoid (4, 5). In contrast, type 2 11βHSD (11βHSD2) is a high affinity, unidirectional, NAD-dependent dehydrogenase with an apparent K_m for F of 50 nmol/L (2, 3, 6). It is this isozyme that is found principally in mineralocorticoid target tissues such as the kidney and colon, where it protects the mineralocorticoid receptor from cortisol excess. Mutations in the gene encoding this isozyme of 11βHSD are responsible for a heritable form of hypertension, apparent mineralocorticoid excess (7–9), in which cortisol acts as a potent mineralocorticoid.

The distribution and localization of 11βHSD1 within tissues have been extensively studied in the rat (10). In human tissues, RT-PCR, enzyme activity studies, and Northern analyses have localized 11βHSD1 to glucocorticoid target tissues, such as liver, lung, gonad, cerebellum, and pituitary (1, 11). However, largely due to the lack of specific antisera against human 11βHSD1, the localization of this isozyme within these target tissues remains unknown.

We now report on the characterization of an antibody against human 11βHSD1 and describe the localization of this isozyme of 11βHSD within human liver, adrenal, ovary, decidua, and adipose tissue.

Materials and Methods

Tissue samples

Tissues were obtained in accordance with local ethical committee approval. Adult human liver, adrenal, and adipose tissues were obtained from the Department of Pathology, University of Birmingham (Birmingham, UK). In every case, tissues had been obtained from operative samples (usually partial hepatectomies, normal adrenals at the time of harvesting donor kidneys, and operative adipose tissue samples) and were histologically normal. Samples of normal human ovary and decidua were also obtained from operative samples from the Birmingham Womens' Hospital. In each case a minimum of six separate normal tissues were studied, and the results were shown to be consistent.

Synthesis of a human 11βHSD1 antibody

Using hydrophilicity profiles, one region (amino acids 19–33) was selected from the published amino acid sequence of the human type 1 isozyme of 11βHSD (1). This sequence was synthesized as an eight-branched multiantigenic peptide, mixed with Freund's complete adjuvant, and used to immunize a single sheep. An IgG fraction was pre-

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pared from the immune serum by ammonium sulfate precipitation and ion exchange chromatography.

Immunohistochemistry

Five-micron thick formalin-fixed sections of normal liver, adrenal, ovary, decidua and adipose tissue were cut and placed on coated glass slides (Fro-Tissuer pen, The Binding Site, Birmingham, UK). After dewaxing, slides were treated with methanol-hydrogen peroxide (1:1000) to block endogenous peroxidase activity. After washing in phosphate-buffered saline (PBS; 0.05 mol/L; pH 7.6), slides were incubated with polyclonal antibody to human 11βHSD1 (liver, ovary, decidua, and adipose tissue at a dilution of 1:100; adrenal at a dilution of 1:200) in 10% normal swine serum for 1 h at room temperature. Control sections included 1) omission of primary antibody; 2) use of primary antibody preabsorbed with the immunizing peptide at a dilution of 1:500, prepared as described previously (12); and 3) tissues known to be negative for 11βHSD1 expression, for example term placenta. In addition, for the human ovary experiments, immunohistochemical studies were undertaken using an in-house antibody against human 11βHSD2 (at a dilution of 1:50) (12). Secondary antibody, donkey antisheep IgG peroxidase conjugate (1:400), was added to sections for 30 min. Slides were developed using 3,3′-diaminobenzidine and were counterstained with Mayer's hematoxylin.

Western analysis

Western analysis was performed by SDS-PAGE on discontinuous acrylamide gels as previously described (12). Briefly, samples were prepared for loading by denaturing at 95 C in 2% SDS, 10% glycerol, 62.5 mmol/L Tris (pH 6.8), and 0.1% dithiothreitol and electrophoresed at 200 V through 4.5% stacking and 10% resolving gels using the Mini-Protean II Western apparatus (Bio-Rad, Richmond, CA). Ten micrograms of total protein from human liver, decidua, and placenta were loaded per lane, and prestained molecular weight markers (Sigma Chemical Co., Poole, UK) were run in parallel lanes. After electrophoresis, proteins were transferred to Immobilon-P membrane (0.4 μm; Millipore Corp., Bedford, MA), and membranes were blocked for nonspecific binding with 20% nonfat milk-PBS-0.1% Tween-20, then washed briefly in PBS-Tween-20 solution. Membranes were incubated with polyclonal antibody to human 11βHSD1 at a dilution of 1:1,000 (overnight at 4 C), washed with PBS-0.1% Tween-20, and incubated with donkey antisheep IgG peroxidase-conjugated secondary antibody at a dilution of 1:75,000 for 1.5 h at room temperature. Membranes were washed, and protein bands were visualized using the ECL detection kit (Amersham International, Aylesbury, UK) by exposing membranes to x-ray film (DuPont, Stevenage, UK) for 1–10 min. Western blot analysis was also performed using the primary antibody preabsorbed with a 1:500 dilution of the immunizing peptide to demonstrate specificity for 11βHSD1.

Results

Western blot analysis indicated a band of approximately 34 kDa in both liver and decidua, in keeping with the predicted size of 11βHSD1. No band was observed in human placenta. A second band corresponding to approximately 68 kDa was consistently observed in human liver. No bands were seen when Western analysis was carried out using primary antibody preabsorbed with the immunizing peptide (dilution, 1:500; Fig. 1).

Sections of normal human liver stained with the anti-human 11βHSD1 antibody revealed intense staining around the central vein, with less staining around the portal triad comprising the portal vein, hepatic artery, and bile ducts (Fig. 2a). On higher magnification, the staining of 11βHSD1 was found to be purely cytoplasmic (Fig. 2b). No staining was observed when the antibody was preabsorbed with the immunizing peptide at a dilution of 1:500 (data not shown).

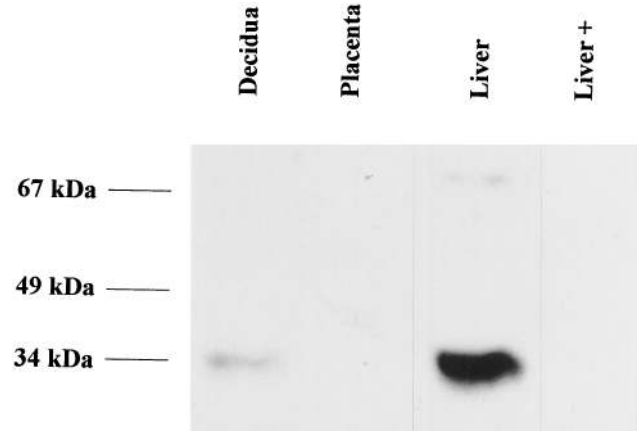

FIG. 1. Western blot showing hybridization to 11βHSD1, a 34-kDa band, in human liver and decidua. In human liver, a second band of 68 kDa was also observed. No hybridization was detected in human placenta or when the primary antibody (1:1000) was preabsorbed with the immunizing peptide at a dilution of 1:500 (Liver +).

No 11βHSD1 immunoreactivity was observed in the human adrenal medulla, but 11βHSD1-immunoreactive protein was detected in all three zones of the adrenal cortex (Fig. 3). Staining intensity appeared to be highest in the zona reticularis > zona glomerulosa > zona fasciculata.

11βHSD1 immunoreactivity was analyzed in human ovary at various stages of the menstrual cycle. Figure 4a shows a group of primordial follicles within the human ovary; the surrounding stroma and the flattened follicular cells surrounding the oocyte were negative for 11βHSD1, whereas the oocyte expressed 11βHSD1-immunoreactive protein. As the primordial follicle developed into a primary follicle, the follicular cells proliferated, but these cells and the surrounding thecal cells remained negative for 11βHSD1 expression, although the oocyte continued to express 11βHSD1 (Fig. 4b). In the mature preovulatory follicle, no 11βHSD1 immunoreactivity was observed in the thecal or granulosa cells (Fig. 4c), in contrast to 11βHSD2 immunoreactivity, which was clearly evident in these two cell layers (Fig. 4d). After ovulation, the luteinized granulosa cells expressed high levels of 11βHSD1 (Fig. 4e). The specificity of the signal was confirmed using the primary antibody preabsorbed with the immunizing peptide at a dilution of 1:500 (Fig. 4f).

Expression of 11βHSD1 was also observed in human decidual cells (Fig. 5) and human omental adipose tissue, where immunoreactivity was localized to both stromal cells and the cytoplasm of differentiated adipocytes (Fig. 6).

Discussion

The isozymes of 11βHSD play a crucial role in modulating corticosteroid hormone action at a prereceptor level. Although 11βHSD1 was the first enzyme to be characterized and cloned in rodent and human tissues (1, 13), there has been recent interest in the 11βHSD2 isozyme (2), principally because of its role in protecting the mineralocorticoid receptor from cortisol excess (14, 15) and its association with human hypertension (7–9). Several studies, however, have indicated that 11βHSD1 regulates glucocorticoid hormone action in key tissues, such as the liver, gonad, pituitary, brain,

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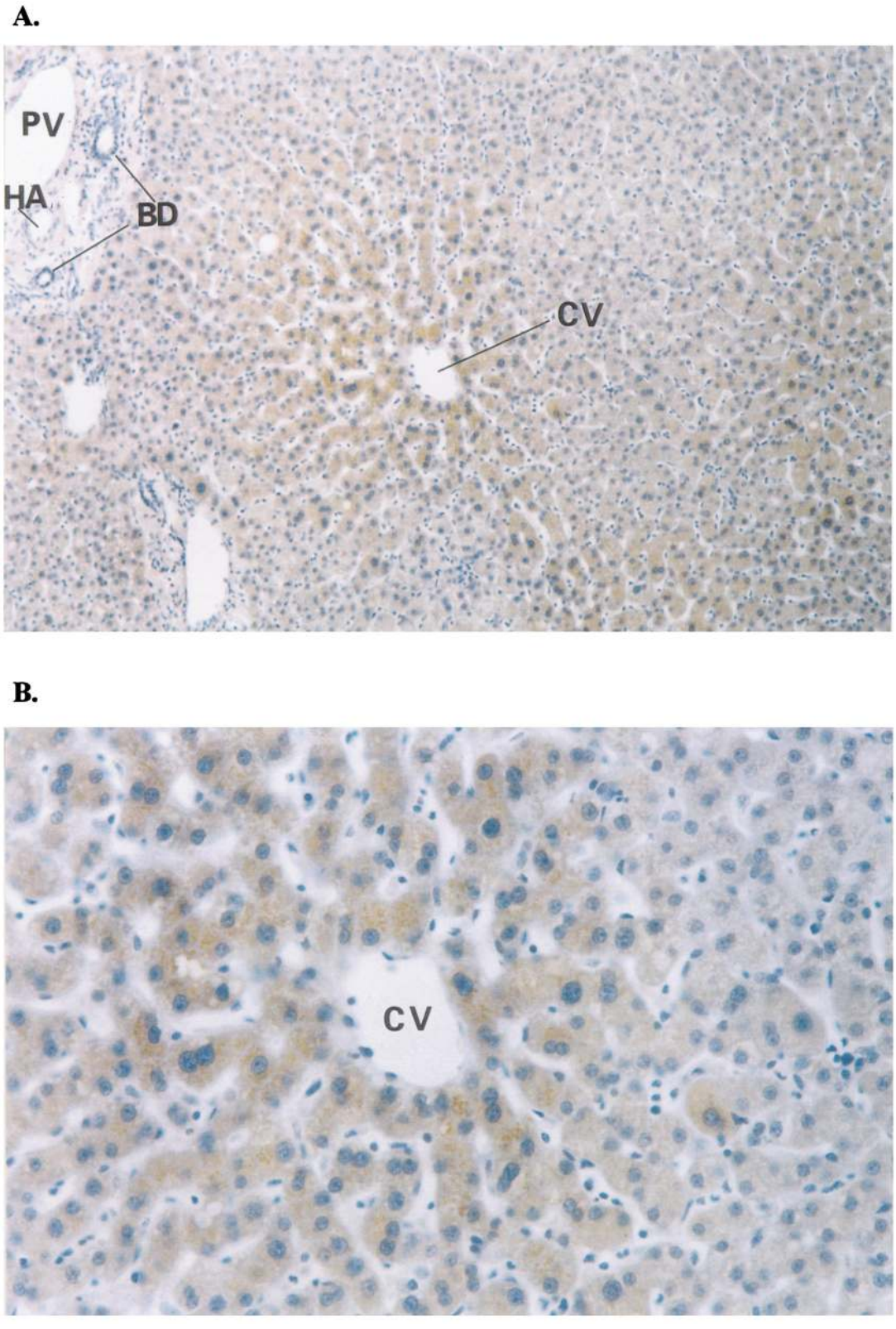

FIG. 2. Expression of 11βHSD1-immunoreactive protein in human liver. A, A section of normal human liver stained with the primary antibody at a dilution of 1:100 (magnification, ×100). CV, Central vein; PV, portal vein; HA, hepatic artery; BD, bile ducts. B, Immunoreactive staining for 11βHSD1 around the central vein. Magnification, ×250.

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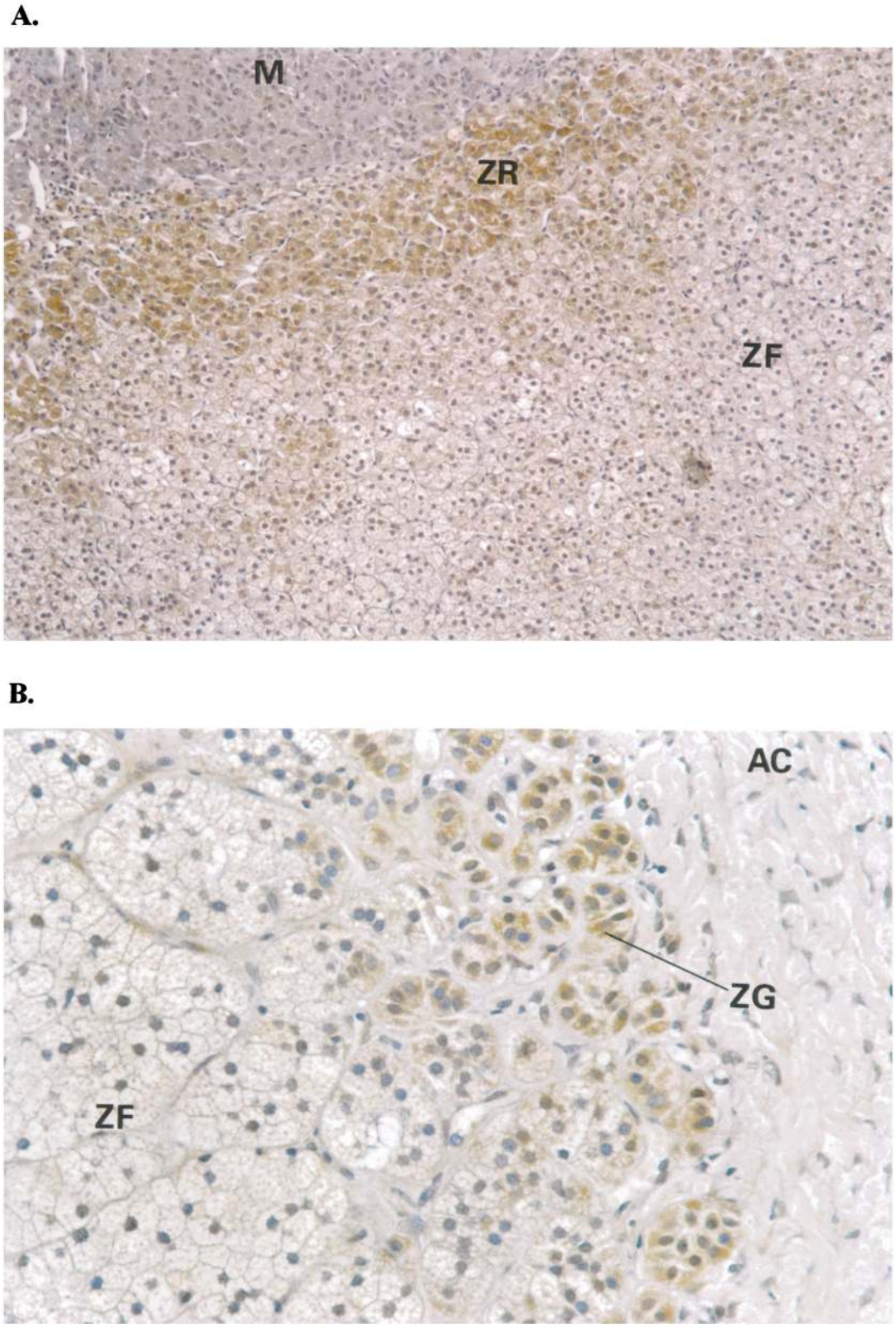

FIG. 3. Expression of 11βHSD1-immunoreactive protein in the human adrenal gland. A, A section of human adrenal stained with anti-human 11βHSD1 antibody at a dilution of 1:200. M, Medulla; ZR, zona reticularis; ZF, zona fasciculata. Magnification, ×100. B, 11βHSD1 immunoreactivity in the zona glomerulosa. ZG, Zona glomerulosa; AC, adrenal capsule. Magnification, ×400.

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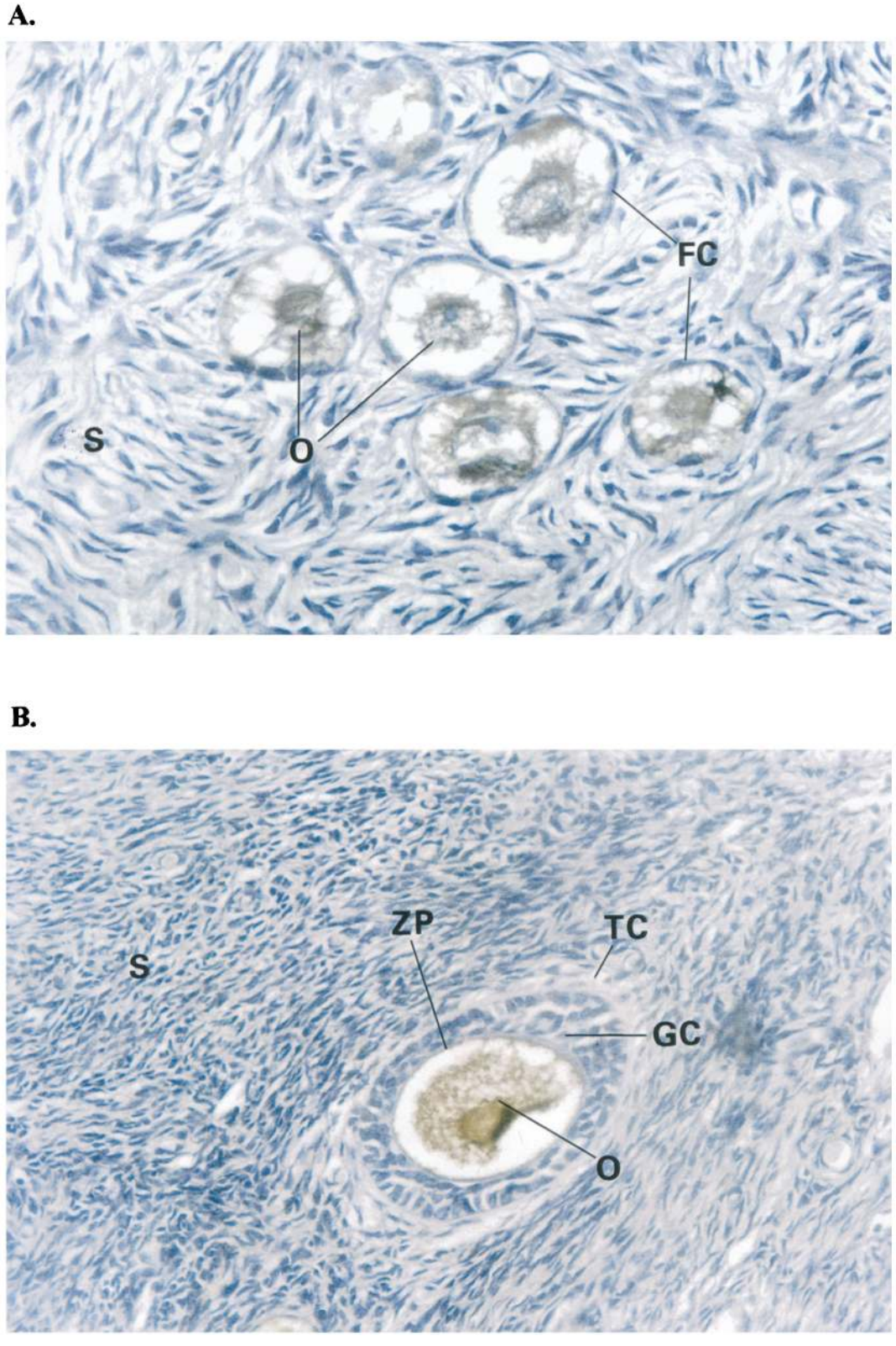

FIG. 4. Expression of 11βHSD1-immunoreactive protein in the human ovary. A, A group of primordial follicles in a section of human ovary stained with the antihuman 11βHSD1 antibody at a dilution of 1:100. O, Oocyte; FC, follicular cells; S, ovarian stroma. Magnification, ×250. B, A primary follicle stained with anti-11βHSD1 antibody. GC, Granulosa cells; TC, thecal cells; ZP, zona pellucida. Magnification, ×250. C, A mature follicle stained with the anti-11βHSD1 antibody at a dilution of 1:100. A, Antrum; GC, granulosa cells; TC, thecal cells. Magnification, ×400. D, Expression of 11βHSD2 in the granulosa and thecal cells of a mature follicle. Anti-11βHSD2 antibody dilution, 1:50; magnification, ×250. E, A corpus luteum stained with anti-11βHSD1 antibody. LGC, luteinized granulosa cells. Magnification, ×400. F, Negative control: primary antibody preabsorbed with the immunizing peptide at a dilution of 1:500. Magnification, ×400.

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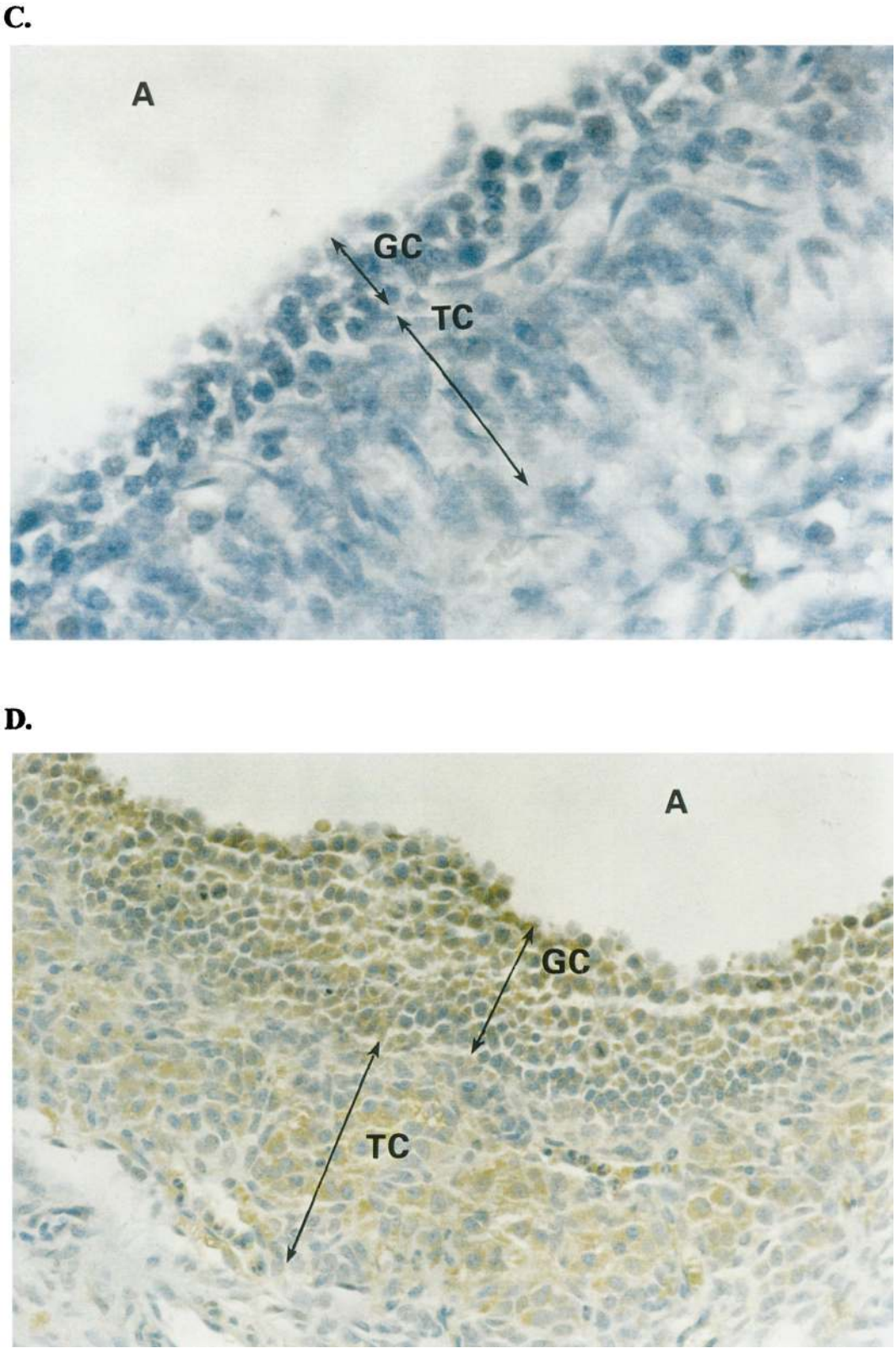

FIG. 4. Continued.

and adipose tissue (4, 16–20). Although 11βHSD1 activity is bidirectional, at least in tissue homogenates with exogenous cofactor added, 11βHSD1 is predominantly an oxo-reductase in intact cell assays (3–5), generating the active glucocorticoids, cortisol and corticosterone, from their inactive 11-oxo metabolites. The development of a specific antiserum against

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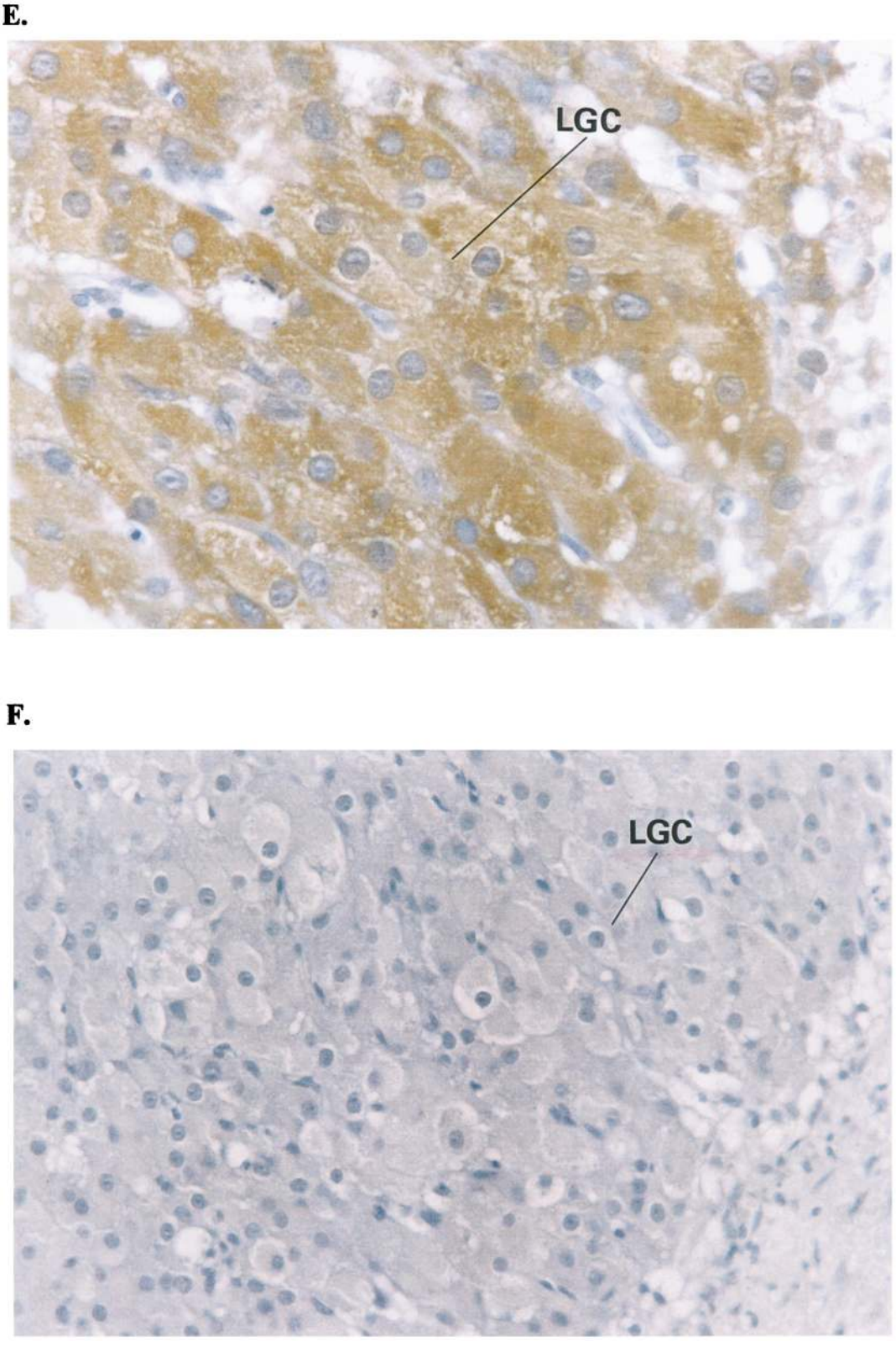

FIG. 4. Continued.

human 11βHSD1 has enabled us to define the localization of this isozyme within human liver, adrenal, ovary, decidua, and adipose tissue, tissues that have been shown to express 11βHSD1 using enzyme activity/messenger ribonucleic acid (mRNA) studies. The specificity of the antiserum was confirmed by demonstrating hybridization to a 34-kDa band, in

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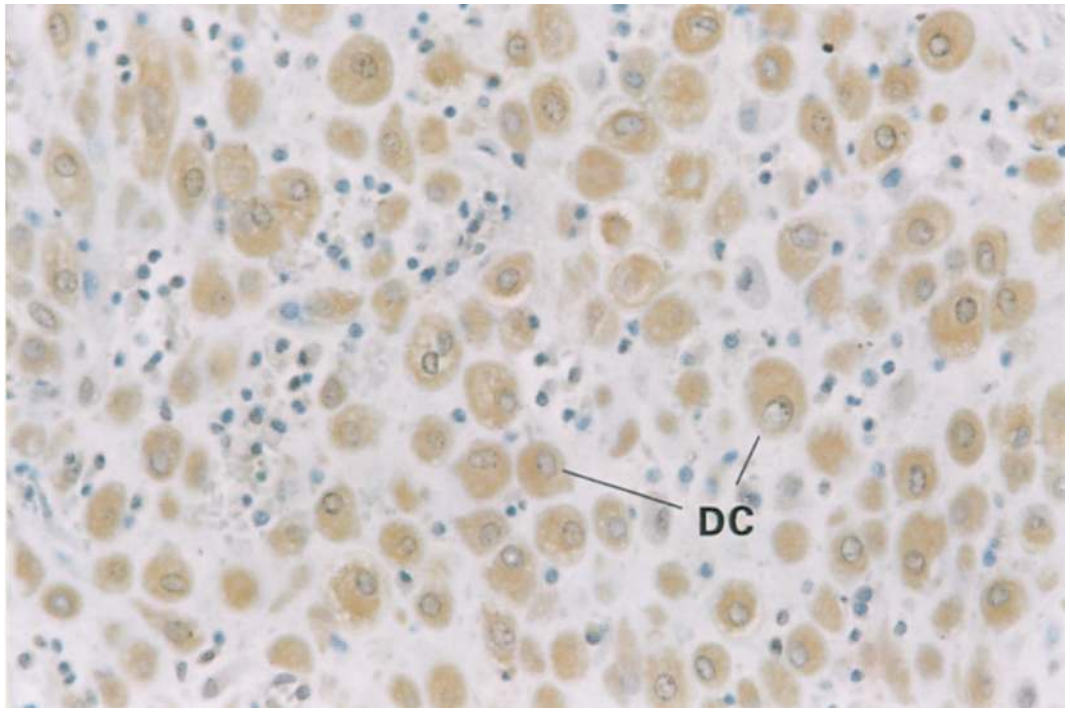

FIG. 5. Expression of 11βHSD1-immunoreactive protein in a section of human decidua. 11βHSD1 immunoreactivity in decidual cells (DC) at a dilution of 1:100. Magnification, ×250.

keeping with the predicted size of human 11βHSD1, in both human liver and decidua. A second band corresponding to approximately 68 kDa was consistently observed in human liver, suggesting that the enzyme may also exist as a dimer in this tissue. Neither the 34-kDa nor the 68-kDa band was observed if the antiserum was preabsorbed with the immunizing peptide.

In the liver, 11βHSD1 expression was observed in hepatocytes radiating outward from the central vein, with no expression around the portal vein, hepatic artery, or bile ducts. The liver is a continually regenerating organ, with migration of hepatocytes from the portal triad toward the central vein upon differentiation (21), and it is possible that 11βHSD1 expression is closely linked with hepatocyte maturation. Functionally, glucocorticoids and 11βHSD1 activity are known to regulate gluconeogenesis within the liver, principally through the rate-limiting enzyme phosphoenolpyruvate carboxykinase (4). Clinically, after an oral dose of cortisone acetate, cortisol rapidly appears in the peripheral circulation (22), in keeping with localization of the type 1 isozyme to hepatocytes around the central vein.

Perhaps more puzzling is the expression of 11βHSD1 in the adult human adrenal, with 11βHSD1 immunoreactivity present in the zona reticularis and less expression in the zona glomerulosa and zona fasciculata. Although it is possible that the apparent reduced staining in the zona fasciculata reflects an artifact caused by the intense lipid content of this zone of the adrenal cortex, these studies are in keeping with our earlier observations in the rat adrenal (23), where we documented 11βHSD1 expression in the zona reticularis. Although glucocorticoid and mineralocorticoid receptors have been observed in the human adrenal cortex, the roles of these receptors and 11βHSD1 in adrenocortical function are unknown. In the zona reticularis, 11βHSD1 may maintain high glucocorticoid concentrations at the cortico-medullary junction required for the induction of phenylethyl *N*-methyl transferase and adrenaline synthesis (24). In the rat zona glomerulosa, it has been suggested that cortisol may inhibit aldosterone formation (25), but such studies need to be confirmed in man.

In human ovary, expression of 11βHSD1 was seen in the oocyte and luteinized granulosa cells of the corpus luteum, but no expression was found in the follicular, granulosa, or thecal cells of the preovulatory follicle. This contrasted with 11βHSD2 immunoreactivity, which was localized to the preovulatory granulosa and thecal cells. Expression of 11βHSD1 in the oocyte and corpus luteum has been demonstrated previously in the rat ovary (26); subsequently, Michael *et al.* (27) showed that human luteinized granulosa cells express 11βHSD1 mRNA and activity. Tetsuka *et al.* (28) have recently shown that human preovulatory granulosa cells express 11βHSD2 mRNA, and that the corpus luteum expresses 11βHSD1 mRNA. These data suggest that luteinization switches on the expression of 11βHSD1 in the second half of the ovarian cycle. Why the corpus luteum, whose main product is progesterone, should express an enzyme whose main role is to generate glucocorticoid is unclear. One possibility may be that cortisol generated *in situ* inhibits LH-stimulated steroidogenesis in the luteinized granulosa cells (27). Alternatively, the role of ovarian 11βHSD1 may relate not to glucocorticoid, but to the metabolism of progesterone. Earlier studies showed that 11-hydroxylated progesterone derivatives have a higher specific activity for 11βHSD than cortisol itself (29), suggesting that

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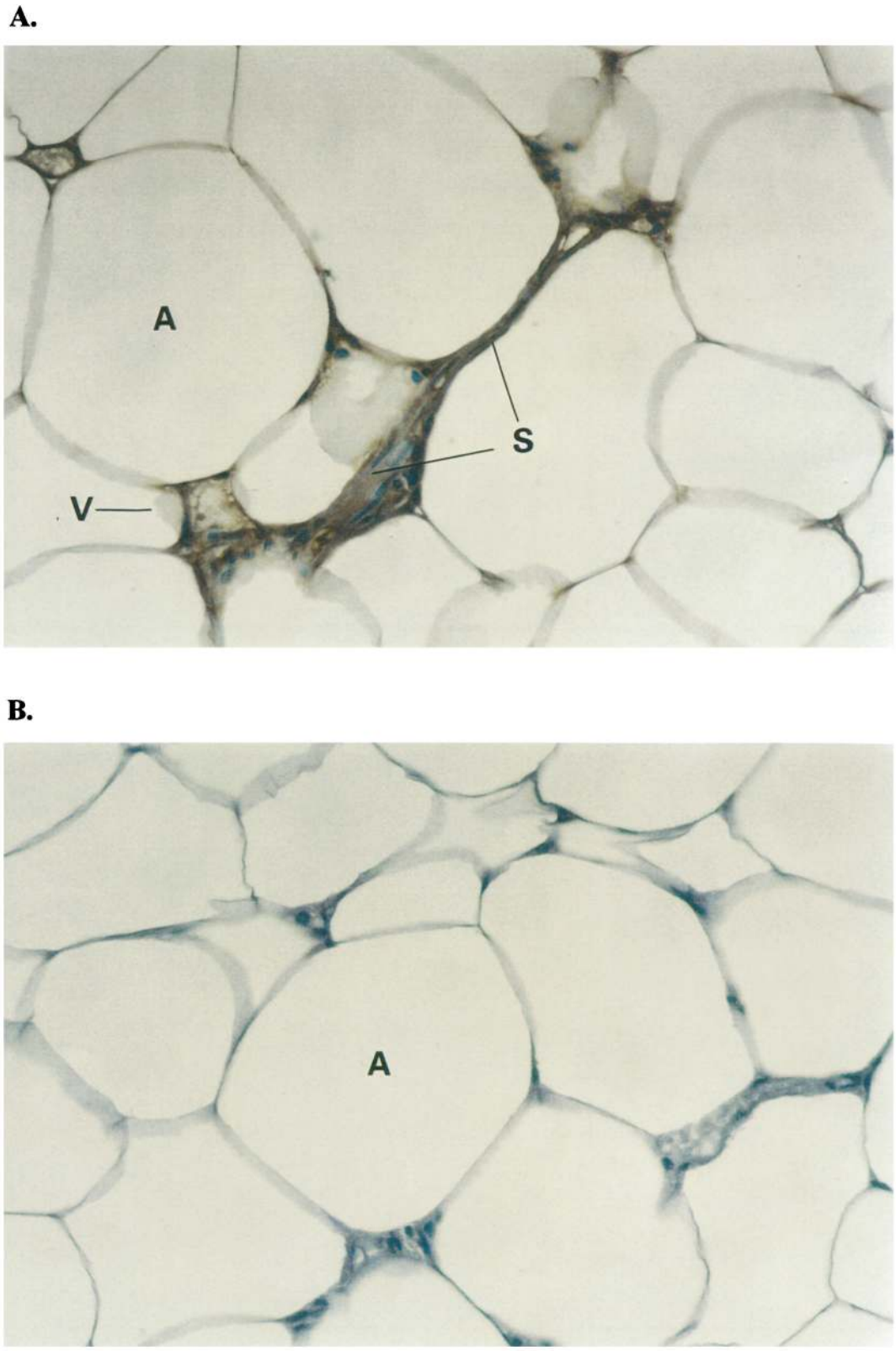

FIG. 6. Expression of 11βHSD1-immunoreactive protein in a section of human omental adipose tissue. A, 11βHSD1 immunoreactivity in adipose tissue at a dilution of 1:100. A, Adipocyte; S, stromal cell; V, venule. Magnification, ×250. B, Negative control: omission of primary antibody. Magnification ×250.

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the preferred substrate for 11βHSD1 may be progesterone or its derivatives. It is unlikely that 11-hydroxylated progesterone derivatives are present in the ovary, as the ovary does not express 11β-hydroxylase, but progesterone itself may be metabolized by 11βHSD1, although this has yet to be demonstrated. Other 11-oxo-steroids, such as 11β-hydroxyandrostenedione, are known to be present in follicular fluid (30), and these could also be putative substrates for 11βHSD1. If cortisone is the endogenous substrate, these studies would suggest that cortisol is critical for maturation of the oocyte, and further studies are required to address the issue of 11βHSD isozyme expression and the outcome of *in vitro* fertilization-embryo transfer techniques (31).

Human decidual cells, formed from endometrial stromal cells after implantation of the blastocyst, express abundant levels of 11βHSD1, in keeping with the findings of earlier mRNA and activity studies (32, 33). The developing blastocyst is semiallogenic and is at risk of immune rejection. Local immunosuppressive activity exists within the decidua (34), and cortisol, via 11βHSD1 expression, may modulate this by inhibiting the production of antiinflammatory cytokines, such as IL-1 (35).

Finally, as exemplified in patients with Cushing's syndrome and in patients treated with corticosteroids, adipose tissue is an important glucocorticoid target tissue. The glucocorticoid receptor is known to be expressed at this site (36), and glucocorticoids exert profound effects on adipocyte function and differentiation (37). Immunolocalization of 11βHSD1 within omental adipose tissue is in keeping with our recent mRNA/activity studies in which we suggested that this isozyme may play a pivotal role in regulating glucocorticoid-mediated adipocyte differentiation and function, with obvious ramifications for the pathogenesis of central obesity (20).

In summary, a novel antiserum against 11βHSD1 has provided us with further information about intracrine control of glucocorticoid action within key human glucocorticoid target tissues. The oxo-reductase activity of this isozyme, generating cortisol from cortisone, suggests important functional roles for glucocorticoid at these sites, with the regulation of 11βHSD1 expression within these tissues being a key modulator of glucocorticoid hormone action.

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Hormones and the Heart
Naples, Italy
September 24–26, 1998

Conveners: Gaetano Lombardi (Naples, Italy) and Luigi Saccà (Naples, Italy)

Speakers: G. Lopaschuk (Edmonton, Canada). W. H. Dillman (San Diego, CA). I. Klein (New York). K. Ojamaa (Manhasset, NY). P. Ladenson (Baltimore, MD). C. Ridgway (Denver, CO). L. Wartofsky (Washington, DC). E. Ghigo (Turin, Italy). S. Anker (London, United Kingdom). P. S. Douglas (Boston, MA). Ä. Hjalmarsson (Gothenburg, Sweden). R. H. Böger (Hanover, Germany). G. Johannsson (Gothenburg, Sweden). D. Johnston. (London, United Kingdom). E. Ambrosioni (Bologna, Italy). M. Metra (Brescia, Italy). M. Chiariello (Naples, Italy). A. Pinchera (Pisa, Italy).

Topics: Thyroid hormone and the heart. Cardiovascular role of GH/IGF-1. Role of renin-angiotensin-aldosterone system antagonists and beta blockers in heart failure.

Deadline for abstract submission is 15 June 1998. Prizes will be awarded to three abstracts, which will also be selected for oral presentation.

This meeting will be of prime interest to all those conducting basic and clinical research in cardiology, endocrinology, angiology and metabolic diseases.

For further details and registration/hotel/abstract forms please contact: Jean Gilder Congressi srl. Via Quagliariello 35/E, I-80131 Naples, Italy. Tel: +39-81-546-3779. Fax: +39-81-546-3781. E-mail: jgcon@tin.it.