MINIREVIEW

Regulation of Steroid Hormone Action in Target Cells by Specific Hormone-Inactivating Enzymes (43356A)

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Abstract. **The target cell sensitivity of steroid hormones is determined by the concerted action of specific hormone receptors and steroid-inactivating enzymes. In recent years, a considerable amount of knowledge has been obtained on hormone receptor concentration-based target cell sensitivity. However, an equal understanding of the role of specific steroid-inactivating enzymes in hormone action is absent. This review highlights the importance of specific steroid-inactivating enzymes in the control of target cell sensitivity of mineralocorticoids, glucocorticoids, androgens, and estrogens. Two classes of enzymes that are actively involved in this process are hydroxysteroid dehydrogenases and hydroxysteroid sulfotransferases. Some of the target cells in which the critical roles of these enzymes have been extensively characterized are those of the kidney, endometrium, and liver. cDNA for many of these enzymes have already been cloned, and rapid progress in the elucidation of this component of steroid hormone action is anticipated.** [P.S.E.B.M. 1992, Vol 199]

Endocrinology as a discipline may have its origin in the discovery of Berthold, who, in 1849, demonstrated that testicular implants devoid of any neural connection are capable of maintaining normal comb growth in castrated roosters. This observation led to the search for blood-borne regulatory chemicals produced by the "ductless glands," chemicals later named "hormones" by Sterling. The first steroid hormone was isolated from the urine of pregnant women and crystallized by Doisy and Butenandt in 1929. For more than a century since Berthold's original publication, endocrinologists have concentrated their efforts on the investigation of circulating levels of hormones and the endocrine glands that secrete these regulatory chemicals. Studies of hormone action at the level of the target cells did not pick up much momentum until discovery of the estrogen receptor by Jensen and Jacobson in 1961 (1). Immediately thereafter, receptors for other steroid hormones, such as androgens, progesterone, and corticosteroids, were identified and characterized (2–6). All of these later events took place during the period that coincided with the explosion of our knowledge of the molecular biology of gene regulation. It was initially suspected that steroid hormone receptors were gene regulatory proteins, a hypothesis that later proved to be correct (7). Therefore, most of the emphasis on steroid hormone action was placed on the hormonal activation of the receptor proteins and their subsequent role as transregulators of target genes. Although these studies have provided some exquisite details of the steps involved in steroidal regulation of target cell sensitivity at the genetic level, the role of certain nonreceptor components in hormone action has largely been overlooked. One of these underappreciated classes of regulators of target cell sensitivity is specific steroid-metabolizing enzymes. At the level of target cells, the role of enzymes that activate a prohormone such as testosterone to its more potent form, 5α-dihydrotestosterone (8, 9), or conversion of the androgen (testosterone) by aromatase (10) to estradiol, has been better appreciated than has the protection of a target cell for one particular type of hormone against its

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physiological agonist or antagonist. This review will, therefore, be concerned with the present understanding of the role of specific steroid-inactivating enzymes in the regulation of target cell sensitivity and will highlight the concept of a dual mechanism of hormone responsiveness, based on the programmed expression of receptor genes and the hormonally regulated expression of genes for steroid-inactivating enzymes. The basic outline of the overall concept is depicted in Figure 1.

Inactivation of Glucocorticoid in Mineralocorticoid Target Cells

Definitive evidence that specific steroid-inactivating enzymes play a key role in the determination of target cell sensitivity first came from the resolution of the apparent paradox of cross-reactivity between physiological glucocorticoid, cortisol, and corticosterone, and the mineralocorticoid aldosterone (11, 12). The Type I ("mineralocorticoid") receptor present in the mineralocorticoid target cell (e.g., kidney, brain, parotid, and colon) has almost identical affinities for both glucocorticoids and the mineralocorticoid. However, within physiological concentrations, glucocorticoids do not act as mineralocorticoids. This was found to be due to the presence of the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) in the mineralocorticoid target cell. This enzyme is responsible for converting cortisol and corticosterone to cortisone and dehydrocorticosterone, respectively. The latter two steroids have a very weak affinity for the mineralocorticoid receptor. Thus, the presence of this enzyme protects the mineralocorticoid target cell from the high circulating level of glucocorticoids. The importance of such a protective action for 11βHSD is underscored by the fact that a congenital deficiency of this enzyme in humans is responsible for the syndrome of apparent mineralocorticoid excess (13, 14). Apparent mineralocorticoid excess is characterized by persistent hypertension and is a potentially fatal disease. Ingestion of large quantities of licorice also causes transient hypertension, mimicking a pharmacological model for apparent mineralocorticoid excess (15). It has recently been established that the active ingredient of licorice, glycyrrhetinic acid, is a potent inhibitor of 11βHSD (16).

Thus, no compensatory mechanism, in the case of either chronic or acute deficiency of 11βHSD, can prevent the mineralocorticoid target cell from being overwhelmed by glucocorticoids in the absence of this critical steroid-inactivating enzyme.

Inactivation of glucocorticoids in the testis by 11βHSD appears to serve a function different from that in the mineralocorticoid target tissues. Activation of the glucocorticoid receptor system in Leydig cells of testes inhibits testosterone synthesis. Low prepubertal levels of 11βHSD in the Leydig cell and temporary saturation of this enzyme during conditions of stress in the adult suppress testosterone synthesis (17, 18).

High activity of 11βHSD has also been detected in the placenta, lung, and liver (19–22). In the placenta, this enzyme may serve a protective role by preventing developmental disturbances in the fetus resulting from maternal glucocorticoid fluctuations during stress. In the lung, it is hypothesized to regulate intracellular glucocorticoid levels during development. The liver is considered to be the major site for metabolic clearance of glucocorticoid hormones.

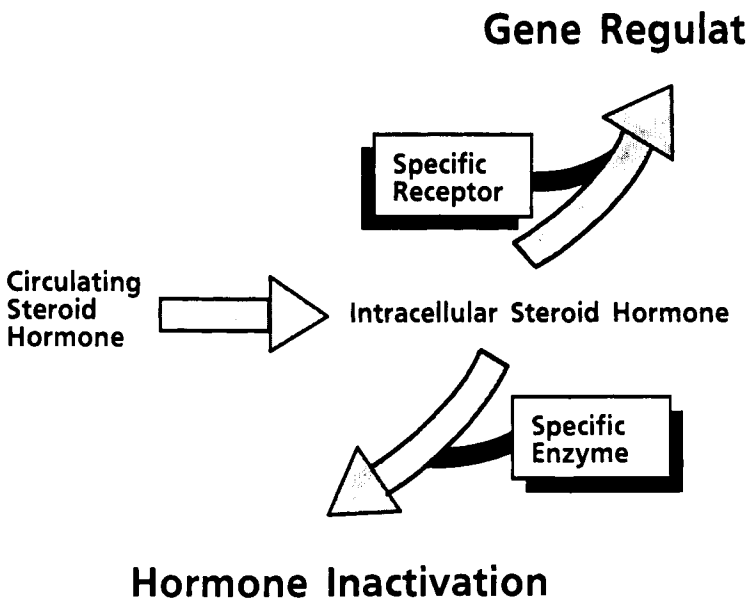

Figure 1. Dual control of target cell sensitivity. After the steroid hormone enters the target cell, it either interacts with a specific steroid receptor and influences gene regulation or can be converted to a receptor-inactive form by specific steroid-metabolizing enzymes. The intracellular ratio of hormone receptor to hormone-inactivating enzyme ultimately determines the target cell sensitivity for a steroid hormone.

Regulation of Estrogen Action by 17β-Hydroxysteroid Dehydrogenase

Intracellular conversion of the most potent physiological estrogen, estradiol, to an inactive (or very weakly active) estrogen, estrone, by 17β-hydroxysteroid dehydrogenase (17βHSD) is one of the regulatory mechanisms that modulates estrogen action in the target cell (23). 17βHSD uses NAD/NADP as a cosubstrate and is capable of acting on both biologically active estrogen (estradiol) and androgens (testosterone and 5α-dihydrotestosterone), converting them to estrone and androstenedione/5α-androstenedione, respectively. Although this enzyme has been detected in many target tissues, including the uterus, placenta, liver, testes, and prostate (23–30), its role in hormone action has been most extensively explored in the endometrial tissue. During the first half of the menstrual cycle, the endometrial cells undergo rapid proliferation that is hormonally driven by the estrogen. Once the necessary morphological features of the endometrium are established, further cell proliferation needs to be arrested and the differentiated function conducive to implantation is achieved by secretion of various gene products from the endometrial structures. These two phases (i.e., proliferative and secretory) of the endometrial cycles are regulated through a hierarchy of neuroendocrine controls originating in the hypothalamus and descending to the ovary via pituitary gonadotropins. Although the circulating level of estradiol is relatively high throughout the menstrual cycle (>30 pg/ml), physiologically high levels of progesterone are achieved only after the midcycle with the formation of the corpus luteum, a transient endocrine gland that is primarily involved in progesterone secretion. Thus, during the second half of the cycle (i.e., the secretory phase), arrest of estrogen-mediated cell proliferation is essential for the expression of the differentiated function. This is achieved via two progesterone-dependent events. First, the intracellular level of the estrogen receptor (ER) is down-regulated to less than 20% of that found in the proliferative phase (30). Because an 80% reduction of the ER still leaves a potentially high estrogenic activity, the second component of the regulatory system involves intracellular inactivation of the estrogenic steroids. More than a 10-fold increase in the intracellular level of 17βHSD in the secretory phase, compared to the proliferative phase of the menstrual cycle, allows rapid conversion of estradiol to estrone, which is a weakly active metabolite. In addition to humans, a progesterone-mediated increase in endometrial 17βHSD has been reported in all other mammalian species examined so far. The antiestrogenic effect of progesterone via changes in the intracellular level of biologically active estrogen is also mediated through the induction of another enzyme, i.e., estrogen sulfotransferase, which sulfurylates estradiol (31). The significance of the estrogen sulfotransferase in overall regulation of estrogen sensitivity in the uterus and in the liver is discussed below.

Regulation of Estrogen and Androgen Sensitivity by Specific Sulfotransferases

The complementary role of estrogen/androgen sulfotransferases and estrogen/androgen receptors in the regulation of target cell sensitivity is clearly illustrated by the temporal changes in androgen responsiveness of the rat liver during maturation and aging, and in the estrogen responsiveness of the uterus during the estrus/menstrual cycle. The temporal pattern of estrogen responsiveness of the uterine endometrium has already been described. The liver of the rat, irrespective of the animal's sex, goes through three distinct phases of androgen sensitivity (32). Hepatocytes of the prepubertal animals are androgen insensitive; androgen sensitivity appears during puberty (~40 days) and reaches a peak level at about 85–100 days. A gradual and time-dependent decline in hepatic androgen sensitivity begins at about 150 days and the liver of animals older than 750–800 days becomes completely androgen insensitive. Androgen sensitivity of the rat liver can be monitored by the androgen-dependent expression of certain target genes such as α_{2u} globulin. We have recently shown that these three phases of hepatic androgen sensitivity correlate with the programmed expression of the androgen receptor mRNA (33). The androgen receptor mRNA is expressed only in the liver during young adulthood and is absent during both prepuberty and senescence. Furthermore, we have also discovered that the liver does not depend solely on modulation of the androgen receptor gene expression for maintenance of its triphasic pattern of androgen sensitivity. A tightly coupled secondary regulation based on enzymatic inactivation of the steroid ligands plays an important role in this process. The key enzymes involved in the secondary regulation appear to be estrogen and androgen sulfotransferases. Estrogen can act as a potent antiandrogen in the liver (34), and both estrogen sulfate and androgen sulfate are receptor inactive (35). Specific sulfotransferases catalyze sulfurylation of the hydroxyl groups of these steroids with the help of a cosubstrate: phosphoadenosinephosphosulfate. We have purified both estradiol sulfotransferase (EST) and dehydroepiandrosterone sulfotransferase (DST) from the liver, produced monoclonal antibody to these enzymes and cloned the respective cDNA. Utilizing the antibody and cDNA probes, we have examined both the temporal and spatial expression of EST and DST in the liver in relation to hepatic androgen sensitivity. The pattern of temporal expression of androgen receptor, EST, and DST during the life-span of the male rat and its relationship to hepatic androgen sensitivity are illustrated in Figure 2. The androgen insensitivity of both prepuberty and senescence is maintained through a combination of at least three known regulatory processes: (i)

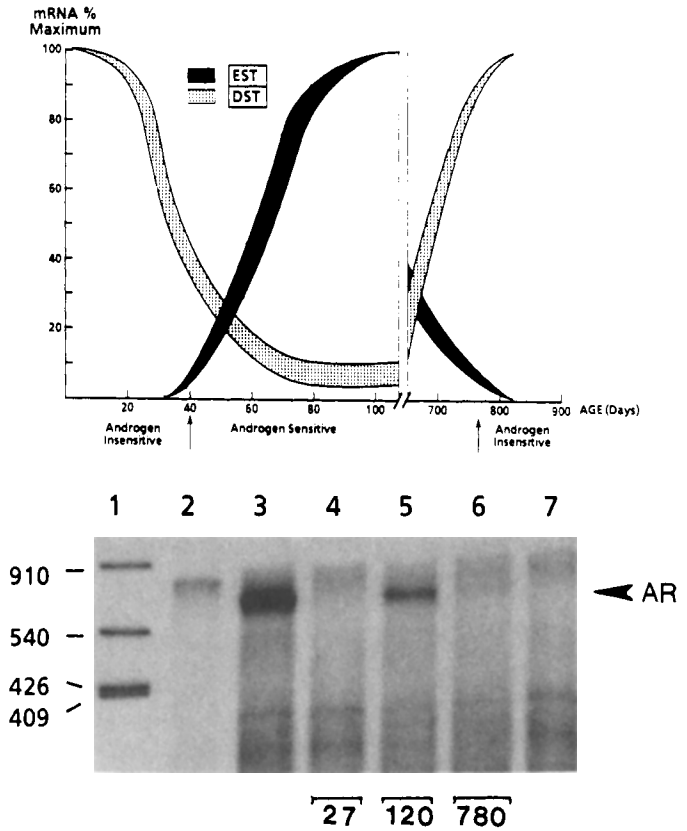

Figure 2. Triphasic regulation of hepatic androgen sensitivity in the male rat by coordinated expression of mRNA for the androgen receptor and androgen/estrogen-inactivating enzymes. (Top) Schematic pattern of expression of estrogen sulfotransferase (EST) and androgen sulfotransferase (DST) during prepuberty, young adulthood, and senescence. (Bottom) The hepatic expression of the androgen receptor mRNA (AR) during these three phases of life (Lanes 4, 5, and 6, derived from livers of 27-, 120-, and 780-day old rats). Androgen receptor mRNA was detected by RNAase protection assay. Other lanes in the figure represent standards and controls (1, size markers; 2, undigested probe; 3, prostate RNA as a positive control; 7, tRNA as a negative control).

down-regulation of the androgen receptor gene expressions; (ii) up-regulation of the androgen sulfotransferase (DST), which causes inactivation of any available intracellular androgen; and (iii) down-regulation of estrogen sulfotransferase, which allows the antiandrogenic effect of the estrogen to prevail. On the other hand, during the androgen responsive phase of young adulthood, not only is the androgen receptor gene turned on, but the pattern of expression of both estrogen sulfotransferase and dehydroepiandrosterone sulfotransferase is totally reversed. Available intracellular estrogens are inactivated by the up-regulation of the EST gene and the androgenic steroids are protected from sulfurylation by down-regulations of the DST gene. The temporally programmed expression of the androgen receptor gene is the primary event, and the contrasting up- and down-regulation of the EST and DST genes appear to be complementary secondary control mechanisms. This is indicated by the fact that, in the liver, both EST and DST are under androgenic regulation; i.e., EST mRNA is induced by androgen, whereas the DST is repressed by the same hormone.

The opposing temporal regulation of EST and DST as seen during the androgen-sensitive and -insensitive phases of life is also reflected in a spatial fashion within the lobular unit of the liver (36). The centrally located hepatocytes within the hepatic lobule (centrolobular) and peripherally located hepatocytes (periportal) have distinctly different patterns of expression of EST and DST with corresponding differences in androgen sensitivity. Immediately after puberty, when the liver begins to acquire androgen sensitivity, only hepatocytes that are located around the central vein begin to express the androgen-responsive genes. These centrolobular hepatocytes, which are first to acquire androgen sensitivity, also express high levels of EST with the concomitant repression of DST, while the periportal hepatocytes, which are still androgen insensitive, express high levels of DST and a negligible level of EST. When the liver becomes highly androgen sensitive (85–100 days), EST is expressed at a high level throughout the hepatic lobule and only less than 10% of the prepubertal level of DST is expressed in the periportal hepatocytes. This pattern is reversed again during senescence. Both the temporal and the spatial pattern of expression of these two sex hormone-inactivating enzymes and their concordance with the hepatic androgen sensitivity provide an interesting example of the coordinated enzymatic regulation

of the sex hormone responsiveness within a target tissue.

In addition to the enzymatic regulation of the androgen sensitivity of the liver, the estrogen sensitivity of the uterus, a major target of the female sex hormones, is also influenced by the estrogen sulfotransferase. Several reports have shown a strong correlation of nuclear estrogen receptor, plasma levels of estrogen, and estrogen sulfurylation activity of the endometrium during the estrous cycle (27–31). In the case of the pig, although the plasma level of estrogen remains relatively high (50–150 pg/ml) throughout the cycle, a high level of nuclear estrogen receptor was detected only during the first 4 days of the 19 days of the estrous cycle, when the rate of estrogen-mediated cell proliferation is seen to be at a maximum. Thereafter, a rapid drop (more than 90%) in the nuclear ER in the endometrium with a concomitant and almost equivalent rise in the estrogen-sulfurylating activity was observed. That is to say, a 10-fold decline in the nuclear ER is accompanied by an equivalent increase in estrogen sulfotransferase during the diestrous period. Thus, despite a physiologically high circulating level of estrogen, the endometrial sensitivity of the hormone is almost completely nullified by down-regulation of ER and up-regulation of the EST, the specific inactivator of the ER ligand.

As illustrated in Figure 3, similar to the pig, estrogen sulfate in the human endometrium is almost undetectable during the proliferation phase of the menstrual cycle and a high level of estrogen sulfate can first be detected during the secretory phase, when cell proliferation has ceased and nuclear ER has fallen below 20% of the proliferative level. Other target tissues that express EST include placenta, corpus luteum, mammary, testis, and adrenal cortex (37–41). It is, therefore, apparent that a coordinated regulatory process involving control of the hormone receptor gene and the genes for hormone-inactivating enzymes is widespread among various target tissues across the species barrier and constitutes an important component of the hormonal regulation of cell function.

Nuclear Localization of the Receptor-Sparing Enzymes and Its Possible Implication in Steroid Hormone Action

Immunostaining of liver sections with monoclonal antibody to estrogen sulfotransferase has consistently demonstrated random, but selective, nuclear localization of EST. Although nuclear localization of other receptor-sparing enzymes such as 11βHSD and 17βHSD has also been observed in target tissues such as the kidney and endometrium, these results were either dismissed as cytoplasmic contaminations or interpreted as immunocytochemical artifacts, as are often encountered with polyclonal antiserum (42–44). However, results published by Pollow *et al.* (26) showing a 7-fold higher 17βHSD activity in human endometrial nuclei as compared with cytosol derived from secretory endometrium certainly deserve an alternative interpretation. In the same context, contrary to the polyclonal antiserum used by Rundle *et al.* (44) for localization of 11βHSD, our results with the monoclonal antibody to EST showing nuclear localization also suggest that nuclear localization of all of these steroid-inactivating enzymes in various target cells should be taken seriously. In order to extend these observations, two further important issues need to be addressed. First, is there any physiological significance of the nuclear localization of the steroid-inactivating enzymes? Second, how does the enzyme translocate into the nucleus? With respect to the first question, it is easy to conceptualize that the major arena for the activity of steroid receptors is in the nucleus, and, in order to maximize efficiency, these enzymes would have to move into the nuclear compartment to neutralize the steroid ligands. Otherwise, once the steroid receptor complex entered the

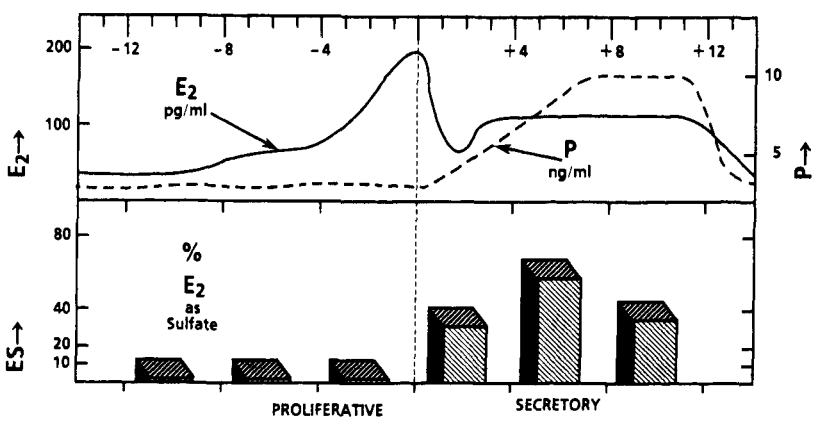

Figure 3. Endometrial estrogen sulfurylation during proliferative and secretory phases of the menstrual cycle. Estrogen sulfurylation activity during the proliferative phase is almost undetectable. However, the activity rises rapidly after ovulation during the secretory phase of the cycle. The nuclear estrogen receptor content of the endometrial cells during the secretory phase is reduced to less than 20% of the level detected in the proliferative phase. Abbreviations used in figure: E2, estradiol; P, progesterone; ES, estrogen sulfate. This figure is based on original data from Refs. 27 and 30.

nucleus, a perpetual steroid action would occur. The mechanism of translocation, however, is less obvious. We have cloned and sequenced the cDNA of the EST and, from the corresponding amino acid sequence, we did not find any putative nuclear translocation signal. Thus, selective translocation of EST into the nuclei on the basis of its own structural motifs appears unlikely. However, it has been established that the ER accepts estradiol in the hormone-binding pocket primarily by interacting with the A ring of the steroid, whereas the active site interaction of EST appears to take place with the D ring of the hormone (35). Because both the ER and EST have comparable binding affinity for estradiol (K_d and K_m both in the nM range), one estradiol molecule can likely act as a temporary cross-linker between the enzyme and the receptor. It is possible that such a heterodimer can migrate into the nucleus on the basis of the nuclear translocation signal of the ER. If this type of transient cross-linking mechanism operates to translocate the EST into the nucleus, sulfation of the estrogen after translocation will dissociate the complex and the enzyme will be trapped in the nuclei. Although further studies are needed to critically examine this model, from a regulatory standpoint scavenging of free steroid hormone within the nucleus provides an important physiological advantage, i.e., prevention of a protracted stimulation of steroid responsive genes without a continued cytoplasmic input.

Hormonal Regulation of Steroid-Inactivating Enzymes in Target Cells

I have already stated that the regulatory role of steroid-inactivating enzymes in hormone action, in most cases, serves as a secondary mechanism; the primary control is the expression of the respective receptor gene. Thus, it can be envisioned that developmentally determined expression of steroid receptors in various target tissues will retain a hierarchical control over the expression of the ligand-inactivating enzymes. A body of information is presently available on the hormonal regulation of 17βHSD, EST, and DST (31, 45, 46). Both 17βHSD and EST in endometrial cells are clearly under progesterone induction. However, the overall regulatory mechanism may be somewhat more complex. This is indicated by the observation that induction of EST activity *in vitro* in endometrial minces requires both estradiol (10^{-8} M) and progesterone (10^{-6} M) (31). The paramount importance of progesterone in the induction of EST in the endometrium is indicated by the fact that progesterone is the only effective therapeutic agent for endometrial adenocarcinoma and regression of the tumor is almost always associated with induction of EST. Unlike the uterus, where EST is induced by progesterone, in the rat liver, this enzyme is induced by androgen. Although we have not yet characterized the regulatory region of the EST gene, it is interesting to note that, in most other cases, both progesterone and androgen receptors utilize the same response element for the activation of the target genes. In human breast cancer cells, there appears to be a positive correlation between the estrogen receptor and EST activities. ER^+ cells generally have a much higher (5- to 10-fold) EST activity than do the ER^- cells (46). Furthermore, tumors that are positive for both estrogen and progesterone receptors contain a level of EST activity about three times higher than that of tumors that are positive for only ER. It is, therefore, possible that a high level of EST in the ER^+ cells may represent an unsuccessful attempt of the cellular homeostatic process to dampen the rate of estrogen-mediated cell proliferation in the mammary gland.

Other Enzymes with Potential Involvement in Target Cell Sensitivity

From this review, it is apparent that conversion of steroid hormones to their receptor inactive form is an important regulatory mechanism for hormone action in target cells. Although most of this article has been concerned with hormone inactivation through oxidoreduction (23, 47) and sulfurylation (48), there are many other enzymatic reactions that can potentially be used to inactivate steroid hormones. One such reaction is hormone-specific glucuronidation, which has not been examined carefully (49). In addition, sulfurylation of the steroid hormone can also serve as a storage form of the hormonal steroid, and its reactivation through specific steroid sulfatases may contribute to an efficient hormonal homeostasis (49, 50). Specific estrone sulfate sulfatase and dehydroepiandrosterone sulfate sulfatase have been identified in breast cancer cells, endometrium, hypothalamus, pituitary, and liver (48–54). A possible physiological role of estrone sulfate sulfatase in estrogen action is indicated by a marked rise of this enzyme activity in the uterus at the end of gestation (54). An enhanced estrone sulfate sulfatase activity and a reduced EST activity during this period may produce a local estrogenic environment in the uterus that is conducive to parturition (54, 55).

Our knowledge of the role of steroid receptors in target gene regulation has advanced greatly. However, a full comprehension of steroid hormone action will remain on the horizon until we achieve a thorough understanding of the enzymes involved in this process.

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