REGULATION OF β-ADRENERGIC RECEPTORS BY STEROID HORMONES

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INTRODUCTION

Adrenal steroid hormones and catecholamines play central roles both in maintaining survival in times of stress and in regulating normal physiologic responsiveness. The interplay between these two hormonal systems is of great physiological importance. Whereas catecholamines exert highly specific effects on specific tissues, steroid hormones have rather broad effects upon many physiologic functions in many tissues. The general pattern observed is one of steroid hormone-induced refinement or regulation of catecholamine-mediated processes. In this chapter we review what is known about the mechanisms by which adrenal steroid hormones regulate the action of the β-adrenergic receptor–adenylate cyclase system. Effects on the α-adrenergic receptors and the effects of gonadal steroids are not addressed (13, 29).

PHYSIOLOGIC MANIFESTATIONS OF STEROID-INDUCED β-ADRENERGIC RECEPTOR REGULATION

Steroid hormones enhance several β-adrenergic actions at the tissue level. Myocardial β_1-adrenergic responses such as positive inotropism (3, 25), posi-

tive chronotropism (20), and increased arrhythmogenicity (20) are enhanced by steroid hormones (29). Steroid hormones facilitate catecholamine stimulation of both hepatic glucose production (17) and glucose uptake by muscle (42). Vasodilation mediated by β_2-adrenergic action is also enhanced by steroid hormones (1, 4).

Steroid enhancement of β_2-adrenergic receptor action in the lung is of particular interest in view of the simultaneous use of steroids and catecholamines in asthma and related pulmonary disorders. Chronic administration of catecholamines results in a fall in the bronchodilatory response to catecholamines (9, 13). This phenomenon of diminished responsiveness is referred to as tachyphylaxis, desensitization, or refractoriness. In intact, tachyphylactic human lung, as well as in isolated tachyphylactic human bronchial muscle, hydrocortisone restores responsiveness to subsequent catecholamine challenge (9, 23). Similarly in dogs, methylprednisolone reverses the state of bronchial tachyphylaxis (48).

MECHANISMS OF β-ADRENERGIC RECEPTOR REGULATION

Research over the past decade has documented two major modes of β-adrenergic receptor regulation that appear to contribute to the regulation of tissue sensitivity to catecholamine action. Steroid hormones participate in both forms of regulation. The first form of β-adrenergic receptor regulation is regulation of the number of receptors in plasma membranes. A wide variety of factors regulate the concentration of these receptors (13, 30). The concentration of receptors can be regulated by translocation of receptors from the plasma membrane to intracellular compartments (46) or by altering rates of synthesis or degradation. Steroid hormones regulate the number of β-adrenergic receptors on cells (see below; 12). Direct demonstration of steroid effects on the rate of transcription of receptor genes has not yet been demonstrated.

The second major mechanism for regulation of β-adrenergic receptor function concerns the regulation of the "coupling" of the receptors to their effectors, the adenylate cyclase system. Steroid hormones have been found to regulate these coupling processes (see below; 14). In order to understand this form of receptor regulation, it is necessary to understand something about the mechanisms by which the receptors are normally coupled to the adenylate cyclase system. It is thought that hormone receptors first interact with a special class of guanine nucleotide regulatory proteins variably referred to as N_s or G/F (because they appear to mediate the stimulatory effects of both guanine nucleotides and fluoride ion on the enzyme) (12, 29, 39). Interaction of the receptors with the nucleotide regulatory protein is promoted by the prior interaction of agonists with the receptors (16). R-N_s interaction leads to

conformational changes in N_s, accompanied by the dissociation of GDP, which is ordinarily tightly bound to this protein. GTP binds to this altered form of the nucleotide regulatory protein, thereby promoting its interaction in turn with the catalytic moiety of adenylate cyclase (C). $N_s \cdot GTP \cdot C$ is thought to be the physiologically active form of the enzyme. GTP is cleaved by a GTPase activity resident on the N_s protein (6). This appears to lead to the dissociation of N_s from C, thus terminating the activation of the enzyme and converting the N_s protein to its physiologically inactive state liganded with GDP. The role of the hormone receptor is to facilitate activation of the enzyme by guanine nucleotides acting through the nucleotide regulatory protein (45).

A major clue to the mechanism of adenylate cyclase activation by β-adrenergic receptors was provided by ligand binding data. This came from a careful study of differences between agonist and antagonist binding receptors are revealed by competition binding experiments. Figure 1A shows a typical antagonist competition curve for occupancy of β-adrenergic receptors. Such binding curves can be analyzed by computerized methods based on the law of mass action. Antagonist curves such as that shown in Figure 1A are found to be uniphasic and "steep" (hill slopes ≈ 1) and model best to a single affinity state. Such curves are unaffected by added guanine nucleotides. In contrast, agonist curves such as that for isoproterenol, shown in Figure 1B, model best to two affinity states with the dissociation constants (K_H for higher-affinity and K_L for lower-affinity) being about 100-fold apart. The higher-affinity state accounts for about three quarters of the receptors. When or hypothyroeotides are added, all the high-affinity receptors appear to be converted into low-affinity state receptors which have affinity identical to that of the lower-affinity state seen in the absence of guanine nucleotides (26).

A series of biochemical experiments has indicated that the high-affinity state of the receptor appears to represent a ternary complex of the agonist, the receptor, and the nucleotide regulatory protein (HRN), whereas the low-affinity state appears to represent the binary complex H-R (32, 44, 45). Agonists stabilize formation of the ternary complex and thus promote the activation of the cyclase.

Since the high-affinity form of the receptor appears to be a reflection of formation of the ternary complex HRN, computer modeling of agonist competition curves can be used to assess the extent of formation of this complex in membranes. Any influence that interferes with the coupling of the receptors with the nucleotide regulatory protein decreases the formation or stability of this complex and shifts the agonist competition curve to the right. This is because there is less of the high-affinity form of the receptor formed. This observation has provided a basis for experimentally assessing the efficiency of coupling of receptors with N proteins under the influence of agonists (26, 32, 44, 45). A variety of circumstances—for example desensitization (26, 30, 46)
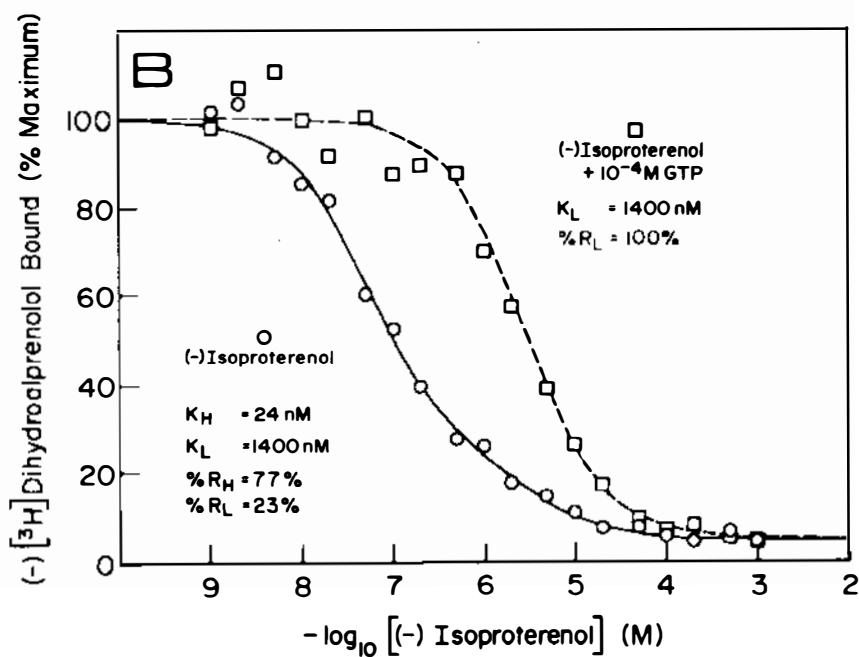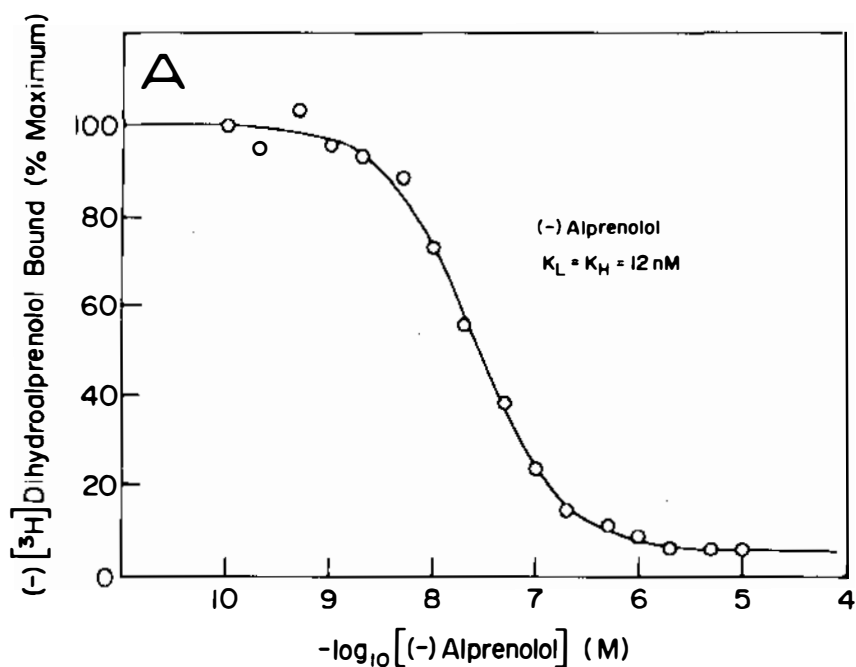
or hypothyroidism (47)—have previously been shown to be associated with impaired coupling of the receptors with the N_s protein. As discussed below, steroid hormones appear to modulate the coupling of receptors with N_s proteins and hence alter the properties of agonist competition curves. In summary, therefore, the steroid hormones regulate both the number and the coupling of the β-adrenergic receptors.

BIOCHEMICAL MANIFESTATIONS OF STEROID-INDUCED β-ADRENERGIC RECEPTOR REGULATION

This section highlights steroid-induced changes in various components of the β-adrenergic receptor–adenylate cyclase system. We address steroid-induced regulation, which applies to most tissues, and note the circumstances in which tissue-specific effects are present.

In Normal Tissues

Most studies involving adrenal steroid hormone regulation of β-adrenergic receptors have been performed with human leukocytes. The initial approach used to was to assess how much cAMP accumulated in response to stimulation by isoproterenol in vitro (27, 33, 37). There was a reproducible "direct" effect (i.e. without added catecholamine) of hydrocortisone to increase cAMP accumulation that was not adequately explained by an alteration of phosphodiesterase activity (33, 35, 37). In addition to this "direct" effect, hydrocortisone increases isoproterenol-stimulated cAMP accumulation (27, 33, 35). Similar hydrocortisone enhancement of isoproterenol-stimulated cAMP accumulation is observed in mast cells (49). When examined directly, isoproterenol-stimulated adenylate cyclase activity is increased 93% in neutrophils exposed in vivo to glucocorticoids (12).

The steroid-induced changes in adenylate cyclase activity are associated with increased receptor binding sites. Oral adminstration of cortisone acetate results in a 39% rise in neutrophil β-adrenergic receptor density (12). Similarly, after two days of oral prednisone therapy, receptor density appears to be elevated in both lymphocytes and granulocytes (41). Glucocorticoids also increase β-adrenergic receptor density in rat lung (34), cultured human lung cells (19),

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Figure 1 Competition curves derived from frog erythrocyte β-adrenergic receptors. A: Antagonist binding. Frog erythrocyte membranes were incubated with [³H]-dihydroalprenolol in competition with increasing concentrations of the β-adrenergic antagonist (−) alprenolol and then assayed for [³H]-DHA binding. Maximum binding represents the binding of [³H]-DHA in the absence of competing (−) alprenolol. The solid line is the computer-generated curve best fitting the observed data points.

B. Agonist binding. Frog erythrocyte membranes were incubated with [³H]-DHA in competition with increasing concentrations of the strong β-adrenergic agonist (−) isoproterenol, in both the absence and presence of 10^{-4}M GTP. Taken from (26).

cultured human astrocytoma cells (18), and in rabbit fetal lung tissues (2, 8). Thus, steroid exposure results in both supersensitization (increased β-agonist stimulation of adenylate cyclase activity) and "up-regulation" of β-adrenergic receptors (increased receptor density).

Once supersensitization and "up-regulation" were demonstrated, attention was directed to potential changes in "coupling" induced by steroid hormones. Receptor "coupling" and high-affinity-state formation were assessed by constructing isoproterenol competition curves as noted above in the section on Mechanisms of β-Adrenergic Receptor Regulation. The ratio of dissociation constants, K_L/K_H, correlates with both the percentage of receptors in the high-affinity state and the intrinsic activity (the maximum ability to stimulate adenylate cyclase relative to isoproterenol) of the competing agent. Thus, the value K_L/K_H can be used as a measure or index of the formation of HRN (i.e. of the "coupling" of receptor occupation to enzyme activation) (14).

After oral cortisone administration to normal human volunteers, the measured K_L/K_H rises from 44 to 130 and the estimated proportion of receptors in the high-affinity state rises from 54% to 80% (14). Moreover, exposure of human neutrophils to hydrocortisone in vitro yields very similar results (14). Thus, glucocorticoids regulate β-adrenergic receptor function by facilitating the formation of the high-affinity "coupled" form of the receptor.

In Desensitized Tissues

Prolonged exposure to endogenous or exogenous catecholamines reduces physiologic responsiveness to subsequent catecholamine stimulation. This phenomenon is known as desensitization (13, 30). Prolonged exposure of β-adrenergic receptors to catecholamine agonists results in three defects: down-regulation (fall in receptor density or number), desensitization (fall in catecholamine-stimulated adenylate cyclase activity), and uncoupling (destabilization of the high-affinity state of the receptor). There may be different time courses for the appearance of each defect, with uncoupling preceding down-regulation at least in some circumstances (22). Further, the relative magnitude of these defects may differ. Thus physiologic desensitization is associated with several biochemical defects in the β-adrenergic receptor–adenylate cyclase system (30).

Since human asthma is a state in which adrenergic receptors are exposed to high concentrations of catecholamines from endogenous or exogenous sources, asthma has been a prime condition under study. Leukocytes from asthmatics appear to have diminished isoproterenol-stimulated cAMP accumulation (10, 28). After exposure to adrenal steroid hormones either in vivo or in vitro, there is a complete or near complete return of responsiveness in isoproterenol-stimulated cAMP accumulation in leukocytes from asthmatics (28, 33). Moreover, prednisone increases β-adrenergic receptor density in lymphocytes and granulocytes obtained from asthmatics (41).

The effects of steroid hormones upon desensitized tissues have been examined in a model of in vitro desensitization of human neutrophil β-adrenergic receptors. The typical pattern of desensitization occurred with reduced cAMP accumulation, decreased receptor density, and uncoupling. The uncoupling is apparent in Figure 2 (15). The curve derived from desensitized cells was shifted to the right of the control curve. This shift to the right was quantitated as an 8-fold increase in the EC_{50} for isoproterenol and was associated with a reduction in K_L/K_H from 120 to 39 (15). Thus exposure of human neutrophils to isoproterenol in vitro results in diminished ability of agonists to stabilize the high-affinity state of β-adrenergic receptors. The effect of steroid hormones was examined in neutrophils simultaneously exposed to isoproterenol and hydrocortisone. The post-exposure (isoproterenol + hydrocortisone) cAMP accumulation was statistically significantly greater than that of cells exposed to isoproterenol alone (15). The β-adrenergic receptor density in the isoproterenol + hydrocortisone treatment group was not different from that of the isoproterenol treatment group. Thus the presence of hydrocortisone attenuates the iso-
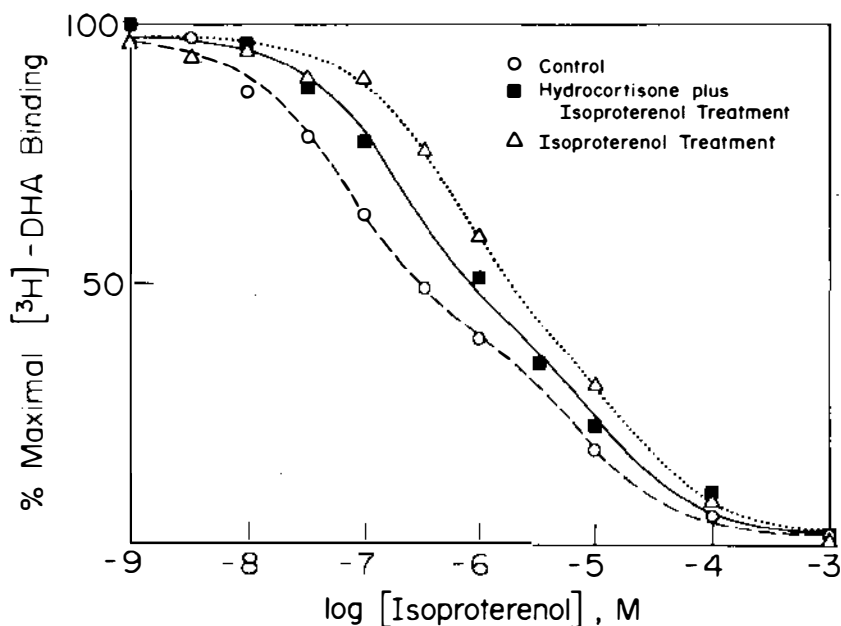
Figure 2 Agonist binding to human β-adrenergic receptors exposed to isoproterenol and hydrocortisone. The abscissa represents the concentration of isoproterenol competing for [³H]-DHA binding to β-adrenergic receptors. The ordinate represents bound [³H]-DHA expressed as a percentage of maximal [³H]-DHA binding. The computer drawn lines represent the best fits to the data. Reproduced from *The Journal of Clinical Investigation*, 1983, 71(3), pp. 565–71 by copyright permission of the American Society for Clincal Investigation.

proterenol-induced desensitization of the β-adrenergic receptor without alter-
ing isoproterenol-induced down-regulation (15).

Altered "coupling" could explain the steroid effect on desensitization while
leaving down-regulation unaltered. "Coupling" was again examined by con-
structing isoproterenol competition curves for receptors derived from neu-
trophils simultaneously exposed to isoproterenol and hydrocortisone. This
resulted in isoproterenol competition curves that were shallow and complex,
lying between the control and the desensitized curves (Figure 2). The resultant
EC_{50} for the isoproterenol + hydrocortisone treatment curve is intermediate
between EC_{50} values for the control and for the desensitized curves (15). The
K_L/K_H determined for the combined treatment curve is also intermediate
between the control and the desensitized values. The effect of hydrocortisone in
combined treatment could be reproduced by prednisolone (15). Thus iso-
proterenol-induced desensitization reduces stability of the agonist-induced
high-affinity state, while the presence of glucocorticoids attenuates this reduc-
tion. These regulatory processes, induced by prolonged catecholamine and
steroid exposure, could allow overall β-adrenergic responsiveness to be very
finely tuned according to physiologic need (15).

In vivo studies also indicate that glucocorticoids modulate β-adrenergic
agonist-induced desensitization but by a rather different mechanism. Oral
terbutaline was used to induce desensitization and down-regulation of β-
adrenergic receptors in lymphocytes derived from normal or mildly asthmatic
subjects. Subsequent administration of a single intravenous dose of methyl-
prednisolone 10 mg kg^{-1} restored the receptor density to pretreatment values
(24). Thus simultaneous in vivo exposure of β-adrenergic receptors to catecho-
lamine and glucocorticoid results in attenuation of the desensitization process
by altering the impaired coupling of the receptors, while consecutive in vivo
exposure of β-adrenergic receptors to catecholamine then glucocorticoid re-
verses the down-regulation. As yet there is no confirmation that a change in
"coupling" occurs after in vivo desensitization followed by resensitization by
steroids. The significance of the different effects of steroids on the desensitiza-
tion process in vitro and in vivo is not yet clear. In both cases, however, steroids
tend to attenuate the catecholamine-induced refractoriness.

Adrenalectomy

We have discussed the effects of exposure to elevated concentrations of adrenal
steroid hormones. Specific changes in the β-adrenergic receptor–adenylate
cyclase system also occur when exposure to adrenal steroid hormones is
reduced through adrenalectomy. These changes may vary from system to
system, however. In the rat myocardium, adrenalectomy results in a reduction
in adenylate cyclase sensitivity to catecholamines and uncoupling without a
reduction in β-adrenergic receptor density (11). Similarly, rat myocardial

cAMP accumulation is reduced after adrenalectomy (38). Adrenalectomy leads to decreased numbers of adipocyte β-adrenergic receptors and reduced iso-proterenol-induced cAMP accumulation (43). Similarly, adrenalectomy results in decreased β-adrenergic receptor density in rat lung membranes (34). The situation in rat liver and brain is somewhat less clear. In contrast to the changes described above, adrenalectomy appears to increase catecholamine-stimulated cAMP accumulation (7, 17), adenylate cyclase activity (5, 31, 50), and β-adrenergic receptor density in rat liver (21, 50). This effect can be abolished by administration of cortisone. A similar adrenalectomy-induced increase in isoproterenol-stimulated cAMP accumulation occurs in the rat brain (36, 40). The reason for these apparently disparate results is not presently known, as no single study has carefully compared changes in rat liver, heart, lung, and brain.

Mineralocorticoids

Relatively few studies have directly examined isolated mineralocorticoid (as opposed to glucocorticoid) effects on the β-adrenergic receptor. However, using the desoxycorticosterone-salt hypertensive rat model, it appears that mineralocorticoid-induced increases in blood pressure are associated with a reduction in β-adrenergic receptor density (51). Information is not available as to whether mineralocorticoids also alter "coupling" or adenylate cyclase activity.

SUMMARY AND PERSPECTIVES FOR THE FUTURE

Exposure to steroid hormones may result in increases in receptor density, enhanced coupling, and enhanced adenylate cyclase activity. At least in rat heart and lung, adrenalectomy appears to result in the converse changes. Further, if reductions in receptor density, coupling, and adenylate cyclase activity are induced through desensitization, steroid hormones may act to return the receptor-cyclase system to a more normal state of sensitivity. This general model seems to apply to several tissues in several species and thus may be quite useful in understanding the biochemical basis for the observed physiologic effects of steroids upon catecholamine action.

There remain, however, many questions concerning steroid hormone effects upon β-adrenergic receptors. The three major unresolved issues are: (a) the mechanisms of the steroid regulatory effects, (b) tissue and species differences, and (c) differences in effects among different types of steroid hormones.

The studies available thus far do not address the question of whether changes in protein synthesis are necessary for the steroid-induced changes in the β-adrenergic receptor–adenylate cyclase system. Moreover, although direct

effects upon the N-site seem to occur, it is unclear whether there is a change in the amount of N-site or whether N-site activity is altered. Since steroid hormones alter pre- and post-receptor events as well as receptor events, it is unknown which effects are relatively most important in normal and abnormal states. Resolving these issues should refine our understanding of receptor biochemistry as well as provide potential new therapeutic approaches.

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