Dexamethasone Regulates the β-Adrenergic Receptor Subtype Expressed by 3T3-L1 Preadipocytes and Adipocytes*

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The subtype of the β-adrenergic receptor expressed in 3T3-L1 preadipocytes and adipocytes differentiated with dexamethasone and methylisobutylxanthine was determined by comparing the affinity of the receptors for epinephrine, norepinephrine, and β-1 and β-2 selective drugs. Receptors in preadipocyte membranes exhibited the same affinity for epinephrine and norepinephrine and bound practolol, a β-1 selective antagonist, 8-fold more avidly than adipocyte receptors. In contrast, adipocyte β-receptors had a 10-fold higher affinity for epinephrine than for norepinephrine and had a 10-fold higher affinity than preadipocyte receptors. Receptors in 3T3-L1 preadipocytes complexed the β-2 selective agonist zinterol with a 20-fold higher affinity than preadipocyte receptors. Hofstee plots and computer analyses of the binding data revealed that the populations of β-1 receptors in preadipocytes and β-2 receptors in adipocytes were nearly homogeneous. Preliminary characterization of the β-receptor phenotype in (nondifferentiating) 3T3-C2 cells treated with dexamethasone and methylisobutylxanthine and 3T3-422A adipocytes differentiated with insulin indicated that the expression of β-2 receptors was not correlated with differentiation, but rather with exposure of the cells to dexamethasone and methylisobutylxanthine.

The regulator of β-receptor subtype was identified as the glucocorticoid analog, dexamethasone, by employing 3T3-L1 adipocytes which were stimulated to differentiate with methylisobutylxanthine and insulin. Detailed binding studies showed that under these conditions the adipocyte receptors retain β-1 character. Subsequent treatment with 0.5 μM dexamethasone promoted the loss of β-1 receptors, the appearance of β-2 receptors, and a net 2- to 3-fold increase in the number of β-receptors. Dexamethasone effected a complete switch from β-1 to β-2 subtype at concentrations as low as 2.5 nM while other steroids were ineffective below a concentration of 10 μM.

determinations of the rank order of potency of several β-adrenergic agonists in promoting the classical physiological effects of catecholamines on heart, adipose tissue, and various types of smooth muscle (2-5). Subsequent studies on the relative abilities of β-adrenergic agents to activate adenylate cyclase or competitively inhibit the binding of a high affinity radioligand to β-receptors in membrane preparations have substantiated and extended this concept (reviewed in Ref. 6). Operationally, β-1 receptors bind prototypic catecholamines with the rank order of affinities isoproterenol > epinephrine = norepinephrine; β-2 receptors sequester the β-agonists with a different but characteristic order of affinities isoproterenol > epinephrine > norepinephrine. The physiological potencies of the β-adrenergic agonists at β-1 and β-2 receptors parallel the binding affinities determined in vitro.

In many species including man, increased heart rate and contractility are controlled principally through β-receptors while bronchial relaxation is effected via β-2 receptors. To achieve physiological target specificity and reduce deleterious side effects, considerable effort has been devoted to the development of β-1 selective antagonists (e.g. practolol, metoprolol) for the treatment of cardiac arrhythmias and angina and β-2 selective agonists (e.g. terbutaline, salbutamol) for the treatment of asthma.

Only a few investigations have addressed the functional specificity, development, and regulation of β-receptor subtypes (7-9). In the central nervous system β-1 receptors appear to be present at noradrenergic synapses while β-2 receptors seem to be localized in non-neuronal cells. In other tissues similar roles have been proposed; β-1 receptors are thought to be concentrated at innervated sites to mediate responses to the neurotransmitter norepinephrine, while β-2 receptors serve principally as binding sites for the catecholamine hormone epinephrine (6). When central noradrenergic neurons are selectively destroyed by chemical neurotoxins the density of β-1 receptors increases markedly while the concentration of β-2 adrenergic receptors remains fixed. Conversely, the chronic administration of antidepressant drugs which elevate norepinephrine levels effects a decrease in β-1 receptor content but has no effect on β-2 receptor levels (7). In addition to their independent physiological regulation, brain β-1 and β-2 adrenergic receptors exhibit separate and distinct patterns of development (8, 9).

Although several reports have described effects of thyroid hormone and corticosteroids on the number and affinity of β-adrenergic receptors (10-12) no systematic studies have been carried out to examine the expression of β-receptor subtypes during cell differentiation and the potential hormonal regulation of β-receptor phenotype in catecholamine responsive cells.

In previous studies (13, 14) we found that 3T3-L1 preadipocytes, which are biochemically and physiologically unresponsive to catecholamines, contain 65% of the number of β-
adrenergic receptors observed in the catecholamine-responsive adipocytes. The receptors on the differentiated and undifferentiated cells exhibit the same $K_D$ (0.2 nm) for $[^{125}]$iodohydroxybenzylpindolol and similar affinities and stereospecificities for $\beta$-adrenergic drugs such as isoproterenol, procaterol, propranolol, and alprenolol. Nevertheless, the possibilities that preadipocytes and adipocytes might possess different $\beta$-receptor subtypes and be subject to different modes of hormonal regulation were neither excluded nor studied.

In this communication we document the differential expression of $\beta$-1 and $\beta$-2-receptor subtypes in preadipocytes and adipocytes using our standard differentiation protocol (15). Furthermore, we have discovered that low concentrations of the hydrocortisone analog dexamethasone elicit the accumulation of $\beta$-2 adrenergic receptors, the loss of receptors with $\beta$-1 character, and a net increase in $\beta$-receptor number of 2- to 3-fold. In addition, the glucocorticoid-induced switch in receptor phenotype apparently affects the efficiency of coupling between the isoproterenol-occupied receptors and other components of the adenylate cyclase system in 3T3-L1 adipocytes.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Differentiation of 3T3-L1 Cells Into Adipocytes—**

3T3-L1 cells and two related cell lines, 3T3-C2 and 3T3-442A, were maintained in cell culture as previously described (14-17). Uniform differentiation of 3T3-L1 preadipocytes into adipocytes was enhanced in one of two ways. Confluent preadipocytes (Day 0) were fed with fresh medium containing 0.5 mm methylisobutylxanthine and either 0.25 $\mu$g of dexamethasone or 5 $\mu$g of insulin. After 48 h, dexamethasone-treated cells were re-fed with drug-free medium while insulin-treated cells were re-fed with fresh medium containing 5 $\mu$g of insulin. Six days after initiating drug treatment (96 h later), $>$85% of the methylisobutylxanthine- and dexamethasone-treated cells were rounded adipocytes and were harvested for membrane preparation. Methylisobutylxanthine and insulin-treated cells were nearly as well differentiated ($>$75% adipocytes). These adipocytes were re-fed again either without or with added 0.5 $\mu$g of dexamethasone and harvested 48 h later.

3T3-442A adipocytes were obtained by treating confluent preadipocytes with 5 $\mu$g of insulin and fresh medium every 48 h for 14 days.

**Preparation of Cell Membranes—** Membranes were prepared from cells as described previously (14). Resuspended membranes were frozen in liquid $N_2$, $\beta$-receptor binding activity and adenylate cyclase activity were stable for at least 6 months.

**Assays—** $[^{125}]$-HYP binding to membranes was measured essentially as described (14) except that 0.1 mm GTP was also present in the incubation mixture. The concentration of $[^{125}]$HYP was carefully monitored and ranged from 300-400 pm for all experiments. Data in each figure were derived from experiments which differ in total $[^{125}]$HYP concentration by less than 10%. The affinities of $\beta$-receptors for various drugs were determined by measuring their ability to competitively inhibit binding of $[^{125}]$HYP to membranes. Data from the competitive inhibition of $[^{125}]$HYP binding are presented as percentages of total specific binding determined as $B_0/B$, where $B_0$ is the specific binding of the radioligand '$[^{125}]$HYP binding in the absence of the indicated concentrations of agonists or antagonists and $B_0 = [^{125}]$HYP binding in the absence of competing ligand. All data were corrected for nonspecific binding. Nonspecific binding, defined as $[^{125}]$HYP binding in the presence of 60 $\mu$g isoproterenol, was usually $<$20% of total binding. Adenylate cyclase activity was determined as described (14). Adenylate cyclase activity was measured in the presence of the indicated concentrations of agonists or antagonists and $B_0 = [^{125}]$HYP binding in the absence of competing ligand. All data were corrected for nonspecific binding. Nonspecific binding, defined as $[^{125}]$HYP binding in the presence of 60 $\mu$g isoproterenol, was usually $<$20% of total binding.

**Computer-assisted Analyses of $[^{125}]$HYP Binding Data—** Data from $[^{125}]$HYP displacement curves were analyzed by the method of Hofstee (18). A computerized iterative analysis of the data was used to resolve nonlinear Hofstee plots into two components (19). The computer program was kindly provided by Dr. Perry Molinoff, University of Colorado Medical Center.

**Materials—** Sources of reagents have recently been listed (14). Practolol hydrochloride was from Ayerst Research Laboratories. Zintol hydrochloride was provided by Mead Johnson. Bovine insulin was obtained from Sigma.

1 The abbreviation used is: $[^{125}]$-HYP, iodohydroxybenzylpindolol.
adipocytes to β-2 receptors on adipocytes is virtually complete (Table I).

Is the Expression of the β-2 Subtype Correlated with Differentiation?—Although the switch in β-receptor subtype occurred during the differentiation of 3T3-L1 cells, it was possible that loss of β-1 character and the expression of β-2 subtype were not related to adipocyte development. Studies on membranes prepared from mature mouse adipose tissue revealed that those adipocytes contained predominantly β-1 receptors.2 Since 3T3-L1 preadipocytes are routinely treated with dexamethasone to elicit differentiation in the absence of corticosteroids. When confluent 3T3-L1 preadipocytes were treated for 48 h with either methylisobutylxanthine alone, dexamethasone alone, or methylisobutylxanthine and dexamethasone together. Measurements of the affinity of the membrane receptors for the β-2 specific drug zinterol disclosed that untreated and methylisobutylxanthine-treated cells contained β-1 receptors while dexamethasone-treated and methylisobutylxanthine- and dexamethasone-treated cells possessed β-2 receptors. Although these initial studies suggested that dexamethasone was the agent responsible for the switch in β-receptor subtype, interpretation of the data was limited by the fact that each of the three treatments ultimately results in a different degree of adipocyte differentiation (15, 24). This complication was eliminated by stimulating adipocyte development in the absence of corticosteroids. When confluent 3T3-L1 preadipocytes were exposed to 0.5 mM methylisobutylxanthine and 5 μg/ml of insulin for 48 h and then refed with drug-free medium containing insulin, the cells differentiated into adipocytes with nearly the same efficiency as observed in the standard differentiation protocol (i.e., after treatment with 0.5 mM methylisobutylxanthine and 0.25 mM dexamethasone; see "Experimental Procedures"). Adipocytes differentiated in the presence of insulin closely resembled standard adipocytes differentiated with dexamethasone in their acquisition of catecholamine-stimulated adenylate cyclase activity (Table I). However, β-adrenergic receptors in membranes derived from adipocytes differentiated with insulin exhibited the binding properties characteristic of the β-1 subtype (Figs. 4 and 5A). After a subsequent 48-h treatment with dexamethasone, β-receptors in these adipocytes clearly displayed the β-2 phenotype as indicated by a 20-fold increase in affinity for zinterol (Fig. 4) and the highly preferential binding of epinephrine as compared with norepinephrine (Fig. 5B). Thus, the treatment...
Regulation of β-Receptor Subtype in 3T3-L1 Cells

TABLE III

Stimulation of adenylyl cyclase by isoproterenol in 3T3-L1 membranes

| Source of membranes | Differentiation protocol | Subsequent treatment | Adenylyl cyclase activity |
|---------------------|--------------------------|----------------------|--------------------------|
| 3T3-L1 preadipocytes | None                     | None                 | 49 53 1.1                 |
| 3T3-L1 adipocytes   | MIX/dexamethasone         | None                 | 28 783 6.5                |
| 3T3-L1 adipocytes   | MIX/insulin              | None                 | 40 316 7.9                |
| 3T3-L1 adipocytes   | MIX/insulin              | Dexamethasone        | 30 262 8.7                |

Adenylyl cyclase activity was determined in membranes from 3T3-L1 preadipocytes and 3T3-L1 adipocytes differentiated either with 0.5 mM methylisobutylxanthine (MIX) and 0.25 μM dexamethasone or with 0.5 mM methylisobutylxanthine and 5 μg/ml of insulin. The adipocytes differentiated with methylisobutylxanthine and insulin were subsequently treated with 0.5 μM dexamethasone for 48 h (see "Experimental Procedures"). Membranes were incubated in a total volume of 55 μl with 5 mM MgCl₂, 20 mM creatine phosphate, 1 unit of creatine phosphokinase, 0.5 mM ATP, 0.5 mM dithiothreitol, 1 mM CAMP, 0.1 mM GTP, and [γ-³²P]ATP (~150 cpm/pmol) in 25 mM Tris buffer, pH 7.4, at 37 °C for 15 min.

TABLE IV

β-Adrenergic receptor number from Scatchard analyses of 3T3-L1 adipocyte membranes

| Source of membranes | Differentiation protocol | Subsequent treatment | K<sub>D</sub> | K<sub>₁</sub> | K<sub>₂</sub> |
|---------------------|--------------------------|----------------------|------------|-----------|-----------|
| 3T3-L1 Adipocytes   | MIX/insulin              | None                 | 1700       | 0.37      |           |
| 3T3-L1 Adipocytes   | MIX/insulin              | Dexamethasone        | 4700       | 0.35      |           |

3T3-L1 adipocyte membranes were incubated to equilibrium at 37 °C with [³²P]HYP over the concentration range of 20-500 nM. Specific [³²P]HYP binding was determined as described under "Experimental Procedures." MIX, methylisobutylxanthine.

Fig. 4. Effects of dexamethasone on β-receptors of adipocytes differentiated with methylisobutylxanthine and insulin. 3T3-L1 adipocytes were obtained by treatment with methylisobutylxanthine and insulin as described under "Experimental Procedures." Cells were refed 48 h prior to harvest and preparation of membranes. Control adipocytes received no drug (ø—ø). Dexamethasone-treated adipocytes received the drug (0.5 μM) for 6 h (ø—ø-ø) or 48 h (ø—ø—ø) prior to being harvested. The change in β-receptor subtype was monitored by measuring the ability of zinterol to displace [³²P]HYP from membranes as described under "Experimental Procedures." The data represent the average of duplicates from assays using a typical set of 3T3-L1 adipocytes.

Fig. 5. Inhibition of [³²P]HYP binding by epinephrine and norepinephrine to membranes from 3T3-L1 adipocytes differentiated with methylisobutylxanthine and insulin. 3T3-L1 adipocytes obtained as described under "Experimental Procedures" were treated for 48 h with 2.5 nM (ø—ø) or 0.5 μM (ø—ø) dexamethasone or received no hormone (ø—ø). The inhibition of [³²P]HYP binding by zinterol was measured as described above.

Fig. 6. Effect of dexamethasone concentration on β-receptor subtype of adipocytes differentiated with methylisobutylxanthine and insulin. 3T3-L1 adipocytes obtained as described under "Experimental Procedures" were treated for 48 h with 2.5 nM (ø—ø—ø) or 0.5 μM (ø—ø) dexamethasone or received no hormone (ø—ø). The inhibition of [³²P]HYP binding by zinterol was measured as described above.

Preliminary Characterization of the Effects of Dexamethasone on 3T3-L1 Cells—Further studies on this effect of dexamethasone were carried out on 3T3-L1 adipocytes obtained from cells differentiated with methylisobutylxanthine and insulin. The change in receptor subtype takes place over many hours. No effect of dexamethasone treatment was detectable after 1 h. After 6 h the affinity of the receptors for zinterol was intermediate between that of β-1 and β-2 receptors and is consistent with a mixed population of receptors (Fig. 4). After 24 h in the presence of dexamethasone computer
analyses showed that 80% of the β-receptors had the properties of the β-2 subtype. By 48 h conversion to the β-2 subtype was complete (Figs. 4 and 5).

In addition to the effect of dexamethasone on the β-receptor subtype, dexamethasone also has a significant effect on β-receptor number. Scatchard analyses of binding data from a typical set of cells (Table IV) show that adipocytes differentiated with methylisobutylxanthine and insulin have approximately 1700 sites/cell whereas subsequent treatment of these cells with dexamethasone for 48 h increased the number of β-receptors to 4700 sites/cell. Receptor affinity for 125I-HYP was not altered under these conditions. The effect of dexamethasone on β-receptor subtype and number is observed at low physiologically effective concentrations of the glucocorticoid analog, e.g. a dose as low as 2.5 nM for 48 h was fully effective in switching the subtype from β-1 to β-2 (Fig. 6).

Effect of the Switch in β-Receptor Subtype on the Activation of Adenylate Cyclase—In order to evaluate the possible consequences of the switch in receptor subtype, the abilities of catecholamine agonists to bind to the β-receptor were compared to their potencies in activating adenylate cyclase. (+)-Isoproterenol was equally effective in competitively inhibiting the binding of 125I-HYP to β-1 receptors in membranes from cells differentiated with insulin and β-2 receptors in cells differentiated with insulin and subsequently treated with dexamethasone (Fig. 7). In contrast, isoproterenol was a potent activator (K\text{\textsubscript{act}} = 6 \times 10^{-8} \text{M}) of adenylate cyclase in cells containing β-2 receptors, while 6- to 10-fold higher levels of the agonist were required to achieve a similar level of stimulation of the enzyme in cells with β-1 receptors (Fig. 8).

**DISCUSSION**

The regulation of the expression of β-adrenergic receptor subtypes has been studied in 3T3-L1 preadipocytes and adipocytes and two closely related cell lines by determining the affinity of the receptor for epinephrine, norepinephrine, and β-1 (propranolol) and β-2 (zinterol) selective drugs. Undifferentiated 3T3-L1 cells possess a significant population of β-1 receptors (14) but are physiologically and biochemically unresponsive to catecholamines (13). When these cells are stimulated to differentiate by standard treatment with methylisobutylxanthine and dexamethasone (15) the resulting adipocytes exhibit an apparently homogeneous population of β-2 receptors (Table I), and concomitantly, acquire high levels of sensitivity and responsiveness to catecholamines (Ref. 13, Table III). The possibility that the appearance of the β-2 phenotype correlated with adipocyte differentiation was inconsistent with parallel experiments that revealed that the methylisobutylxanthine/dexamethasone protocol also elicited the β-1 to β-2 receptor switch in nondifferentiating 3T3-C2 cells. Moreover, the differentiation of 3T3-442A cells in the presence of insulin alone (and the absence of dexamethasone) resulted in adipocytes which retained the β-1 receptor phenotype (Table II).

A definitive determination of the agent responsible for regulating β-adrenergic receptor subtype was achieved using 3T3-L1 adipocytes differentiated in the presence of methylisobutylxanthine and insulin. These adipocytes acquired sensitivity to β-adrenergic agonists (Table III) but retained β-1 receptors (Figs. 4 and 5). Subsequent exposure of these adipocytes to low concentrations of dexamethasone for 48 h caused the loss of β-1 receptors and the appearance of a receptor population exhibiting β-2 character. A survey of the literature indicates that the data presented in this communication constitute the first demonstration of corticosteroid regulation of β-adrenergic receptor subtype.

Dexamethasone treatment also increases the cellular concentration of β-receptors, 3T3-L1 adipocytes differentiated with methylisobutylxanthine and insulin have ~1700 β-1 sites/cell, an amount nearly identical with the number previously reported in 3T3-L1 preadipocytes (14). Subsequent treatment of these cells with dexamethasone yields 4700 β-2 receptors/cell (Table IV). From these observations, it is possible to speculate that the switch in β-receptor subtype does not involve the post-translational conversion of existing β-1 receptors into β-2 receptors (although this is not excluded). In view of the established mechanism of steroid hormone action, it seems more likely that dexamethasone induces the synthesis and/or the accumulation of new β-2 receptors which eventually replace the β-1 receptors as they are removed from the cell surface. Evaluation of this notion will require studies using inhibitors of protein and mRNA synthesis, as well as the covalent labeling and subsequent characterization of the receptors by β-receptor-specific photoaffinity analogs (25). In preliminary studies using cycloheximide, β-1 receptors are removed from the cell surface by 24 h after protein synthesis is inhibited.

Previous studies have described a 3- to 5-fold increase in rat liver β-receptor density after adrenalectomy and the suppression of this effect by the administration of glucocorticoids (10). In contrast, β-receptor density and affinity in human granulocytes were increased in response to cortisone administration (11). Neither of these investigations explored the
possibility that the observation might be attributed to the selective expression (or loss) of β-1 or β-2 receptors.

The concentration of dexamethasone necessary to effect the change in β-receptor subtype and number in 3T3-L1 cells is very low. For example, treatment with 2.5 nM dexamethasone for 48 h is completely effective. Concentrations of 10 μM deoxycorticosterone and progesterone are necessary to elicit the same change in β-receptor subtype, while dihydrotestosterone was ineffective at 100 μM. Dexamethasone at ≤0.25 nM has no effect on receptor number and subtype. These results suggest that the regulation of β-receptor subtype is mediated through glucocorticoid receptors.

Although dexamethasone promotes a switch in β-receptor subtype from β-1 to β-2 in 3T3-L1 and two closely related cell lines, 3T3-C2 and 3T3-442A, the effect is not universal. Dexamethasone has no detectable effect on β-receptor number or subtype in C6 glioma cells which have predominantly β-1 receptors. Thus while more cell lines need to be studied, it appears that not all cells with β-1 receptors are susceptible to regulation of β-receptor subtype by glucocorticoids. On this point, it may be noteworthy that the 3T3-L1, C2, and 442A cell lines are of embryonic origin.

The dexamethasone-mediated switch in β-receptor subtype has several possible physiological and pharmacological consequences. One effect is that the cells become more sensitive to physiological regulation by epinephrine as compared with norepinephrine. In addition, β-1 and β-2 receptors apparently differ in the efficiency of coupling with the adenylate cyclase system. A useful measure of this parameter is the ratio $K_{\text{on}}/K_d$ where the agonist $K_d$ is determined by the inhibition of $^{125}$I-HYP binding and $K_{\text{on}}$ is the concentration of agonist required for half-maximal activation of adenylate cyclase. The lower the ratio the more efficient the coupling of the cyclase components. In 3T3-L1 adipocytes containing β-2 receptors $K_{\text{on}}/K_d = 0.1$ for isoproterenol while adipocytes with β-1 receptors have a ratio of ~1 for the same drugs (Figs. 7 and 8). Data from studies with epinephrine and norepinephrine are consistent with this result. Two speculative explanations are 1) the two subtypes of β-receptor differ in their abilities to interact with the guanine nucleotide binding regulatory component or 2) they differ in their susceptibilities to in vitro desensitization. Although the mechanism responsible for the differential coupling properties of isoproterenol-occupied β-1 and β-2 receptors is unknown the results raise the possibility that glucocorticoids may be capable of modulating the pharmacological responsiveness of some types of cells.

Conclusion—The corticosteroid analog dexamethasone exerts several profound regulatory effects on the β-adrenergic receptor system of 3T3-L1 adipocytes. Treatment of the cells with dexamethasone causes the loss of β-1 receptors, the accumulation of β-2 receptors, a 2- to 3-fold increase in the number of β-receptors, an increased sensitivity to epinephrine, and an apparent enhancement in the coupling efficiency of isoproterenol-occupied receptors. It will be of interest to determine whether the exposure of developing embryos and fetuses to similar doses of dexamethasone will alter the β-receptor subtype, concentration, and properties in catecholamine-sensitive target tissues.

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