Review Article

Small-Molecule Hormones: Molecular Mechanisms of Action

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Small-molecule hormones play crucial roles in the development and in the maintenance of an adult mammalian organism. On the molecular level, they regulate a plethora of biological pathways. Part of their actions depends on their transcription-regulating properties, exerted by highly specific nuclear receptors which are hormone-dependent transcription factors. Nuclear hormone receptors interact with coactivators, corepressors, basal transcription factors, and other transcription factors in order to modulate the activity of target genes in a manner that is dependent on tissue, age and developmental and pathophysiological states. The biological effect of this mechanism becomes apparent not earlier than 30–60 minutes after hormonal stimulus. In addition, small-molecule hormones modify the function of the cell by a number of nongenomic mechanisms, involving interaction with proteins localized in the plasma membrane, in the cytoplasm, as well as with proteins localized in other cellular membranes and in nonnuclear cellular compartments. The identity of such proteins is still under investigation; however, it seems that extranuclear fractions of nuclear hormone receptors commonly serve this function. A direct interaction of small-molecule hormones with membrane phospholipids and with mRNA is also postulated. In these mechanisms, the reaction to hormonal stimulus appears within seconds or minutes.

1. Introduction

Molecular mechanisms of action of small-molecule hormones have been studied for decades. The biological function of these hormones was initially attributed mostly to their extranuclear activities presently referred to as nongenomic; however, the exact mechanisms of such actions were then not known. Subsequently, the majority of efforts were directed towards the clarification of the transcription-modifying function of these hormones bound to their nuclear receptors that are hormone-regulated transcription factors. This generated an enormous amount of information regarding the genomic action of hormones, the identity of their target genes, and so forth. It finally became apparent that the genomic action of hormones is insufficient to fully explain their biological roles, so that the nongenomic mechanisms are again being intensively studied. In this comprehensive paper we present basic information regarding the genomic and nongenomic mechanisms of action of small-molecule hormones, emphasizing the intermediary role of various proteins between the hormonal stimulus and the biological response of the cell. It should be noted, though, that although our current knowledge of the molecular mechanisms of action of these hormones is impressive, not all has been solved and many mechanisms still await explanation.

2. The Genomic Mechanism of Action of Small-Molecule Hormones

“Genomic mechanism of hormone action” refers to the regulation of target gene activity by hormones via their protein receptors, which also possess all the features of a transcription factor. This mechanism engages transcription and translation, and its biological effects are executed by a newly synthesized proteins. The first effects of engagement of this mechanism might be detected 30–60 minutes after its initiation; however, maximal effects are usually observed after several hours.
## Table 1: Selected representatives of the nuclear receptor superfamily.

| Family | Receptor                                           | Ligand                                                                 |
|--------|----------------------------------------------------|------------------------------------------------------------------------|
| I      | Triiodothyronine receptor (TR)                     | Triiodothyronine                                                      |
|        | Retinoic acid receptor (RAR)                       | All-trans-retinoic acid                                               |
|        | Vitamin D receptor (VDR)                           | 1α,25(OH)₂D₃                                                          |
|        | Peroxisome-proliferator-activated receptor (PPAR)  | Polyunsaturated fatty acids, benzopyran, eicosanoids, 15-deoxy-12,14-prostaglandin J₂, thiazolidinediones, other |
|        | Reverse-ErbA (Rev-ErbA)                            | Unknown                                                                |
|        | Retinoic-acid-receptor-related orphan receptor (ROR)| Unknown                                                               |
|        | Liver X receptor (LXR)                             | Oxysterols                                                            |
| II     | 9-cis-Retinoic acid receptor (RXR)                 | 9-cis-Retinoic acid                                                  |
|        | Hepatocyte nuclear factor-4 (HNF-4)                | Acyl-CoA thioesters                                                   |
| III    | Estrogen receptor (ER)                             | 17β-estradiol                                                         |
|        | Androgen receptor (AR)                             | Androgens                                                             |
|        | Progesterone receptor (PR)                         | Progesterone                                                          |
|        | Glucocorticoid receptor (GR)                       | Glucocorticoids                                                       |
|        | Mineralocorticoid receptor (MR)                    | Mineralocorticoids, glucocorticoids                                   |
| IV     | Nerve-growth-factor-induced clone-B (NGFI-B)       | Unknown                                                               |
| V      | Steroidogenic factor-1 (SF-1)                      | Oxysterols                                                            |
| VI     | Germ cell nuclear factor (GCNF)                    | Unknown                                                               |
| 0      | Heterodimerization small partner (HSP)             | Unknown                                                               |

### 2.1. Nuclear Hormone Receptors.

Nuclear receptors of small-molecule hormones belong to the superfamily of nuclear receptors, consisting of receptors for steroid hormones, thyroid hormone, vitamin D, retinoic acid and its derivatives, fatty acids, prostaglandins, and cholesterol derivatives, as well as of “orphan” receptors with unknown ligands. Small fractions of some of these receptors also act outside of the nucleus, in mechanisms generally called “nongenomic”, which are mediated by processes other than a direct binding of the receptor to DNA.

Structural similarities of nuclear receptors allow the subdivision of the superfamily into 7 families/subfamilies (0–VI); families I to VI are quite well defined [56–58], while family 0 contains various receptors, which do not fit into other families (Table 1). Nuclear receptors, although recognizing their own target genes and ligands with high specificity and being either partly or completely devoid of affinity for other genes and ligands, have a similar structure (Figure 1). A typical, full-length nuclear receptor has a variable A/B domain at its N-terminus, followed by a well-conserved DNA-binding C domain, then by a hinge D domain, and by a well-conserved ligand-binding E domain. Some receptors also have an F domain on their C-termini, the function of which is usually unclear.

The A/B domain of many nuclear receptors contains elements involved in hormone-independent transcription activation (AF1). Its function might be modified by phosphorylation, as was shown for the all-trans-retinoic acid receptor (RAR), peroxisome-proliferator-activated receptor (PPAR), orphan Nurrl receptor, estrogen receptor (ER), and so forth [59–62]. The sequence and tridimensional structure of the C domain determine the recognition specificity of the receptor’s target genes. The domain contains two zinc fingers; in each of them four perfectly conserved cysteines keep one zinc ion in place [63]. At the base of the first zinc finger, a P-box is present; its amino acid sequence determines the recognition of a specific (usually hexameric) DNA sequence in the receptor’s target genes. At the base of the second zinc finger, a D-box is located; its sequence is, in turn, responsible for the recognition of the distance between the two hexamers forming the hormone response element (HRE) in the promoter of target gene [64]. In addition, the D-box plays a role in receptor dimerization. The C domain might contain the nuclear localization signal (NLS) or fragments thereof. Next, the D domain contains NLS and facilitates rotation of the DNA-binding domain in relation to the ligand-binding domain. In addition, it contains elements involved in cofactor binding, DNA binding, and in heterodimerization [65]. Finally, the E domain binds a specific hormone, takes part in homodimerization as well as in heterodimerization, and, on its C-terminal end, contains a ligand-dependent transcription activation domain (AF2) [66]. In some cases the E domain might play a role in the active inhibition of transcription. The E domain of the steroid hormone receptors takes part in the binding of heat shock proteins (HSP, chaperone). The structure of this domain is formed by 12 α-helices (H1–H12) and resembles pocket-like hormone-binding site. The sizes, shapes, and charges of this pocket present in various receptors differ from each other, and this why most receptors bind only their own hormones.
with an extremely high specificity and affinity; however, some of them, such as the PPARγ receptor, possesses a large pocket allowing them to bind various ligands [67]. A very important feature of nuclear receptors is that in the absence of the hormone, conformation of their E domains differs from that acquired upon hormone binding [68–70]. The most spectacular is the change of position of the last helix (H12), containing the AF2 domain. Without the hormone, the H12 is moved to the side and protrudes from the rest of the E domain, leaving the empty pocket opened. Upon hormone binding, the H12 comes nearer and closes the hormone inside the pocket [71]. This feature is crucial for the major part of the functions of nuclear hormone receptors, including subcellular localization (as for steroid receptors) and transactivation activity.

The activity of the nuclear receptor might be modulated by various posttranscriptional modifications including phosphorylation, acetylation, methylation, palmitylation, and sumoylation [72–76]. In addition, its biological efficiency depends on the rate of its turnover [77]. Like many other proteins, hormone receptors are degraded mainly by the ubiquitin-proteasome-dependent pathway. To be degraded by the proteasome, proteins must be tagged with multiple ubiquitins. The process of tagging depends on three enzymes acting sequentially; the third one, ubiquitin ligase, determines the specificity of protein ubiquitylation [78]; for example, Hdm2 and carboxyl-terminal HSP70 interacting protein (CHIP) promote degradation of the glucocorticoid receptor (GR) [79, 80]. Blocking receptor degradation by proteasome inhibitors impairs ERα- and progesterone-receptor-(PR-) mediated transactivation but enhances GR-mediated transactivation [81, 82]. Notably, binding of chaperones such as HSPs and associated proteins to steroid hormone receptor prevents receptor ubiquitylation [83, 84]. Calmodulin (CaM) binding to ERα also prevents receptor ubiquitylation and degradation by the proteasome [85, 86], while its binding to AR prevents receptor degradation by calpain [87]. In addition, palmitylation of ERα decreases 17β-estradiol-dependent receptor degradation [88].

2.2. Hormone Response Elements in the Promoters of Target Genes. A classic, genomic mechanism of action of small-molecule hormones is based on the binding of its nuclear receptor to the target gene. Two elements facilitate such an interaction: the DNA-binding domain of the receptor and HRE, a specific sequence in the regulatory elements of the gene. Such sequences (single or multiple) are usually localized close to the basal promoter, not farther than several hundred base pairs in the 5’ direction from the transcription start site (TSS). However, they might also be present in atypical positions, for example, in the enhancers localized even a few thousand base pairs above the TSS. The negative HREs (nHREs) tend to localize close to TSS, sometimes even below this site [89, 90].

Analysis of the natural and artificial HREs showed that nuclear hormone receptors preferentially recognize hexamers, sequences consisting of six nucleotides. Steroid hormone nuclear receptors (family III), with the exception of ER, preferentially bind to the AGAACA sequence, while the remaining receptors, including families I and II receptors and ER, prefer the G/AGGTC/GA sequence [91–93]. Both are consensus sequences and consist of the nucleotides most commonly found at a given position in natural HREs; it is then to be expected that natural HREs very commonly differ from the consensus sequence. HREs usually are formed by two hexamers and, most commonly, nuclear hormone receptors bind to the DNA either as homodimers (mostly, but not exclusively, family III receptors) or as heterodimers (mostly families I and II receptors) [94–99]. The binding of a monomeric receptor to a monomeric or to a dimeric HRE is plausible, as in the case of steroidogenic factor-1 (SF-1, family V) [100], but for “classic” receptors such situations are less common. Depending on the relative position of the two hexamers, dimeric HRE might be a direct repeat (DR), palindromic (PAL), or inverted palindromic (IP) HRE.

HREs for steroid hormone receptors, also called steroid hormone response elements (SREs), are usually palindromes consisting of the AGAACnnnTGTTCCT or of a similar sequences with three neutral (e.g., of any sequence) nucleotides between hexamers. As mentioned above, the exception to this rule is ER which preferentially binds to the G/AGGTC/GAnnnTC/GACCT/C palindrome [64, 101]. Nevertheless, each of these receptors preferentially recognizes its own target SREs with a very high specificity being a result of various factors, such as deviations from the SRE consensus sequence, distinct amino acids surrounding DNA
binding domain fragments of the receptor directly contacting SREs, interactions with other transcription factors bound to their own binding sites in the proximity of SRE, tissuespecific expression of various receptor isoforms, and the level of receptor expression [102, 103]. It should be mentioned that other types of SREs are known, such as a selective androgen response element (ARE) which is not PAL, but DR-type. It has been recently shown that such AREs might be recognized not only by AR, but also by PR [104, 105]. In addition to classic SREs, which mediate transcription activation, a number of negative SREs are known that inhibit the transcription when the steroid-hormone-activated receptor binds to nSRE [106, 107].

Nuclear receptors belonging to the families I and II preferentially bind to the consensus G/AGGTC/GA sequence organized into DR, PAL, or IP [108–111]. The binding to DR drives the strongest biological effect; in fact, natural HREs recognized by these receptors are most commonly DRs. Specificity of the binding is achieved thanks to HRE's configuration, to the number of neutral nucleotides separating the two hexamers, to the sequence of hexamers and of HRE-flanking DNA-fragments, and to the sequence of the receptor DNA-binding domain [112–115]. In DRs, one neutral nucleotide between hexamers (DR1) warrants the binding of RXR/RXR homodimers, of RAR/RXR or of PPAR/RXR heterodimers; two nucleotides (DR2) — the binding of RAR/RXR heterodimer; three nucleotides (DR3)—the binding of VDR/RXR heterodimer; four nucleotides (DR4)—the binding of TR/RXR heterodimer; finally, five nucleotides (DR5) — the binding of RAR/RXR heterodimer. Nuclear receptors for nonsteroid small-molecule hormones also bind to DR0 and to DRs with more than five neutral nucleotides separating hexamers [116, 117] as well as to other nonclassical HREs. In addition, some HREs might be bound by various receptors; for example, the AGGTCATGACCT PAL0 sequence is recognized by Rev-ErbA, retinoic-acid-receptor-related orphan receptor-α (RORα), and for nerve-growth-factor-induced clone B (NGFI-B) orphan receptors [100, 125, 126].

2.3. Regulation of Transcription. On the basis of the molecular mechanism of action and of the subcellular localization in the absence of ligand, nuclear hormone receptors can be divided into two types. In general, type I receptors preferentially reside in the cytoplasm (in unliganded form) and, while in the nucleus, are most active as homodimers. The best known receptors of this type are family III steroid hormone receptors. Type II receptors, after being synthesized and modified in the cytoplasm, in the presence or absence of their ligand, preferentially translocate to the nucleus, where they are most active as heterodimers. The best known receptors of this type belong to families I and II. Binding of nuclear hormone receptors to DNA might result in transcription activation or in transcription inhibition, and such phenomena result from variable molecular mechanisms. Each hormone has a group of target genes which it activates (positively regulated genes) and a group of genes which it inhibits (negatively activated genes) (Figure 2).

2.3.1. Type I Receptors. In the circulation, steroid hormones are bound to transporting proteins. They enter the cell by diffusion or are actively transported by a cell-membrane-bound transporting proteins. The majority of their nuclear receptors, a classic examples of type I receptors, reside in the cytoplasm forming inactive complexes with various proteins, including heat shock proteins HSP70 and HSP90. Formation of such complexes promotes proper folding of the receptor into a conformation allowing steroid binding [127–131]. Upon hormone binding, receptor conformation changes, and this results in the breakup of the complex. The “activated” receptor translocates to the nucleus thanks to its association with chaperones and importins [132, 133], where it binds to its SREs in the promoters of target genes (Figure 3). It is suggested that intranuclear mobility of steroid receptors, some of the most mobile proteins within the nucleus, depends on the presence of chaperone proteins such as HSP90 [134].

Steroid hormone receptors usually bind to DNA as homodimers. Their preferential SREs are palindromes separated by three neutral nucleotides. Occasionally, they might bind to DNA as monomers; in such a case SRE might consist of only one hexamer and is usually preceded by an A- and T-rich sequence, as shown for Rev-ErbA, retinoic-acid-receptor-related orphan receptor-α (RORα), and for nerve-growth-factor-induced clone B (NGFI-B) orphan receptors [100, 125, 126].

![Figure 2: Diagram of transcription regulation by small-molecule hormones. H: hormone, HR: nuclear hormone receptor.](image-url)
Inhibition of transcription by steroid hormones and their receptors is a result of a variety of mechanisms, such as hormone-receptor-complex-dependent inhibition of the activity of other transactivators, for example, activator protein 1 (AP1) and NF-κB [144–146]. In this mechanism, binding of the receptor to DNA is not necessary. A number of nSREs are also known. Binding of a hormone-activated or a hormone-free steroid receptor to nSRE leads to the inhibition of transcription mediated either by corepressors bound to hormone-activated receptor or by another group of corepressors bound to hormone-free receptor. Such interaction results in deacetylation of histones exerted by histone deacetylases (HDACs) and in modification of chromatin structure. In turn, chromatin becomes condensed and inaccessible to transcriptional activators [147–151]. Other molecular mechanisms involved in the inhibition of gene transcription via nSRE are also known, such as competition for a binding site with transcriptional activators [107, 152–154].

2.3.2. Type II Receptors. Families I and II receptor proteins, synthesized and modified in the cytoplasm, have their NLS exposed so they can translocate to the nucleus in the absence of the hormone. Therefore, both hormone-free and hormone-bound forms of the receptor could be present in the nucleus. Since the conformation of the DNA-binding D domain is stable (independent of the hormone), both receptor forms might bind to the promoter of the target gene; this is why type II receptors are able either to activate or to inhibit transcription of the same gene in a hormone-dependent manner.

In contrast to type I receptors, type II receptors usually bind to their HREs as heterodimers. Their universal heterodimerization partner is RXR. Heterodimerization with RXR modulates nuclear trafficking of other receptors [155, 156] and increases both affinity of the other receptor to its HRE as well as its transactivation activity [157–160]. Type II receptors can also bind to DNA as heterodimers with nuclear receptors other than RXR, as homodimers and as monomers [III, 161–163]. In such a case, their affinity for DNA might be lower than that of heterodimers with RXR.

It should be remembered that type II receptors preferentially recognize HREs consisting of two hexamers creating DR, PAL, and IP. In VDR, TR, and RAR heterodimers with RXR, which bind to DR3, DR4, and DR5, respectively, RXR preferentially binds to the first hexamer [164, 165]. On the other hand, in RAR/RXR and PPAR/RXR heterodimers bound to DRI, RXR occupies the second hexamer [166, 167]. The presence of RXR in receptor heterodimers raises the question as to how 9-cis-retinoic acid modifies transcription of other hormones’ target genes. Most probably it has no influence on the level of activation of triiodothyronine (T3) target genes bound by TR/RXR and of 1α,25(OH)2D3 target genes bound by VDR/RXR [168, 169]; however, there are reports claiming otherwise [170]. In all-trans-retinoic acid target genes bound by the RXR/RAR heterodimer, 9-cis-retinoic acid alone does not regulate the activity of such genes, but when both receptors are simultaneously bound to their ligands (9-cis-retinoic acid and all-trans-retinoic acid, respectively), genes are activated synergistically [171]. Finally, when RXR forms heterodimers with a “permissive” partner, such as PPAR, liver X receptor (LXR), or nerve-growth-factor-induced B (NGFI-B) orphan receptor, 9-cis retinoic acid can regulate transcription on its own or act synergistically with the ligand of its partner [172, 173].

In addition to HREs mentioned above, type II receptors bind to numerous untypical HREs and to very common
nHREs. Binding of the hormone-receptor complex to nHRE results in transcription inhibition, so that the recruitment of corepressors preferentially binding to hormone-activated receptor plays here a major role.

Hormone target genes with unoccupied HREs are active on the basal level, which depends on the presence of transcription factors other than hormone receptors. In genes positively regulated by the hormone, the binding of a hormone-free receptor heterodimer to HRE leads to the recruitment of a corepressor complex, which, by deacetylation of histones, leads to condensation of chromatin. This, in turn, hampers the binding of transactivators and of basal transcription factors to DNA; as a result, transcription is inhibited below the basal level (Figure 4(a)) [147, 148, 174–176]. However, upon hormone binding to the receptor, conformation of its ligand-binding domain changes; this results in the dissociation of corepressors, in the recruitment of a coactivator complex containing HATs and in transcription activation markedly above the basal level (Figure 5(b)) [177–189]. In genes negatively regulated by the hormone, transcription inhibition occurs as a result of numerous mechanisms; some of them are still not completely known. The inhibition could be indirect, depending on the binding of hormone receptors to a strong transactivator (such as API, NF-κB, and p53); such binding results either in a blockage of transactivator’s activity or in its binding to DNA [190–192]. In this mechanism, the binding of the receptor to the DNA is not a prerequisite for the inhibition of transcription. In the direct mechanisms, HRE might be present close to or might overlap the binding site for a strong transactivator. Under such circumstances, transcription inhibition is the result either of competition for a binding site, or of binding of the receptor to the transactivator resulting in the repression of its activity [193, 194]. In another direct mechanism, the binding of hormone-activated receptor to nHRE initiates recruitment of specific corepressors preferentially recognizing hormone-bound receptors [149–151, 195–198]. In addition, hormonal receptors bound to nHREs located close to (commonly behind) the transcription start site might affect the binding of type II RNA polymerase to the basal promoter [199].

2.3.3. Interaction of Nuclear Hormone Receptors with Other Proteins. As mentioned above, the biological action of small-molecule hormones depends on their interaction with their receptors, as well as on the interactions of the receptor with DNA and with other proteins. In the genomic mechanism of hormone action, the most important interaction is that of the receptor with coactivators, corepressors, and other transcription factors. On the other hand, in the nongenomic mechanisms, the most crucial role is played by the binding either of the cytoplasmic fraction of nuclear receptors or of hormone itself to extranuclear proteins.

Interaction of Nuclear Hormone Receptors with Basal Transcription Factors. Transcription may occur only in the presence of basal transcriptional machinery, a complex consisting of tens of proteins bound to DNA close to the transcription start site. A typical basal promoter contains a TATA box (TATAA/TAA/T) located 20–30 base pairs above TSS, a sequence recognized by TATA-binding protein (TBP). Some promoters do not have this sequence; however, the basal transcriptional machinery binds to such promoters anyway and at a similar distance form TSS as in the case of typical promoters. Binding of TBP to the basal promoter initiates a cascade of binding of other basal transcription factors. TBP together with TBP-binding proteins (TAFs)
forms transcription factor IID (TFIID). The next step of preinitiation complex formation is the binding of IIB (TFIIB), IIF (TFIIF), and IIH (TFIIH) transcription factors. Finally, type II RNA polymerase is bound, and transcription is initiated. Nuclear hormone receptors interact with the basal transcription factors not only via other proteins (coactivators and corepressors) but also interact with them directly. It has been shown that TR, RXR,RAR, ER, GR, and androgen receptor (AR) might directly bind to TBP, AR and ER—to TFIIF; ER, TR, and VDR—to TFIIB, and so forth [200–205]. It is suggested that such binding might bidirectionally affect (activate or inhibit) the recruitment of the basal transcription factors to the preinitiation complex.

**Interaction of Nuclear Hormone Receptors with Coactivators.** Transfer of information regarding binding of the receptor to HRE and the receptor status (hormone-free or hormone-bound) to the basal transcriptional machinery is usually executed by other proteins that do not bind to DNA but form a functional “bridge”. Such proteins possess various activities. The same coactivator or corepressor complex might bind to several nuclear receptors; some of these complexes might also coregulate transcription initiated by transcription factors of other type.

The first coactivator cloned in humans was steroid receptor coactivator-1 (SRC-1) [179]. Together with TIF-2 (SRC-2) and TRAM-1 (SRC-3, ACTR, and RAC3), it forms the p160 coactivator family. The p160 proteins are indeed coactivators of many nuclear receptors including GR, ER, PR, VDR, TR, RXR, and PPAR [179, 180, 183, 189]. They contain an LXXLL (L: leucine, X: any amino acid) motif, by which they bind to the ligand-binding domain of the receptor activated by the hormone. Importantly, a specific structure of the receptor, first of all of its AF2 domain, is a prerequisite for such interaction [206].

CREB-binding protein (CBP) and p300 possess a histone acetyltransferase activity [207, 208] and are coactivators of various transcription factors, including nuclear hormone receptors [177, 178]. The binding of p300/CBP to the nuclear receptor is hormone dependent and AF2 domain dependent. p300/CBP bind to p160 proteins, to TBP, and to TFIIB basal transcription factors, and, as such, are intermediates between receptors and basal transcriptional machinery. Another coactivator, p300/CBP-associated factor (p/CAF), interacts with
p160, p300/CBP, and hormonal nuclear receptors. It also has a histone acetyltransferase activity [182].

Multiprotein complexes containing thyroid-hormone-receptor-associated proteins (TRAP) or vitamin-D-receptor-interacting proteins (DRIP) have been identified [181, 185]. Both complexes are very similar, if not identical, and consists of fourteen-sixteen 70–230 kDa proteins. Their DRIP205/TRAP220/TRIP2 subunit, by the LXXLL motif, interacts with TR, VDR, and other nuclear receptors such as RXR and RAR [209] in a hormone-dependent and a receptor-AF2-domain-dependent manner. Other components of these complexes interact with the basal transcriptional machinery.

A number of other coactivators interacting with nuclear receptors are known, such as PPARgamma coactivator 1 (PGC-1), which also interact with other receptors, for example, with TR [184, 188] and with activating signal cointegrators-1 and -2 (ASC-1 and ASC-2) interacting with SRC-1, p300/CBP, basal transcription factors, and nuclear receptors [186, 187].

The formation of a coactivator complex is initiated by the binding of hormone-bound receptor to its HRE. This is followed by the recruitment of the coactivator proteins, which directly bind nuclear receptors and by the binding of other proteins. The final multicomponent complex, by modification of chromatin structure and by interaction with the basal transcriptional machinery, activates transcription of target genes.

Interaction of Nuclear Hormone Receptors with Corepressors. Inhibition of transcription is usually achieved by the interaction of the receptor with corepressors [176]. The best known corepressors are nuclear corepressor (NCoR, RIP-13), a large, 270 kDa protein, as well as silencing mediator for retinoic acid and thyroid hormone receptors (SMRT) [147, 148]. Both proteins have several isoforms. Other proteins, such as the small ubiquitous nuclear corepressor (SUN-CoR) and the Alien protein, might also serve as nuclear hormone receptor corepressors [174, 175]. The motif that allows NCoR and SMRT to bind to the receptor is FXI/HIXXXI/L (L: leucine, X: any amino acid, I: isoleucine, and H: histidine) [210, 211]. NCoR and SMRT bind to the families I and II nuclear receptors, to ER and to PR (but not to other members of family III) bound to a specific antagonists, and to some orphan receptors. They also bind to other proteins, including HDACs [212, 213].

Recent developments identified a heterogeneous group of corepressors of a new type. What makes them unique among corepressors is the fact that they bind to the receptor activated by the hormone. The group includes receptor-interacting protein 140 (RIP140) and ligand-dependent corepressor (LCoR). They bind to a various ligand-bound receptors, including ER, GR, PR, and VDR, via the coactivator-specific LXXLL motif, but recruit HDAC proteins and other corepressors [149–151].

Hairless protein (Hr) contains both the hormone-activated-receptor-binding LXXLL motif and a CoRNR box—a sequence mediating the binding of the corepressor to the hormone receptor. When it interacts with ligand-bound ROR, it utilizes the LXXLL motif, whereas when it interacts with VDR, it likely utilizes another domain. On the other hand, Hr interacts with hormone-free TR as a typical corepressor, utilizing the CoRNR box and recruiting HDAC [195–197].

The preferentially expressed antigen in melanoma (PRAME) is expressed in various cancers, but in healthy tissues it is present only in testes, ovaries, endometrium, and adrenal glands. PRAME contains the LXXLL motif and selectively inhibits transcription in the presence of all all-trans-retinoic-acid-bound RAR isoforms. It likely executes this inhibition by recruiting other corepressors [198].

The repressor of estrogen activity (REA) binds to the ER-agonist (e.g., 17β-estradiol) and to the ER-antagonist (e.g., tamoxifen) complexes. By doing so in the presence of agonist, it inhibits the activity of target gene, while in the presence of antagonist it magnifies its action [214]. The suppression by REA is a result of the competition with coactivators for binding to ER, as well as of the recruitment of HDAC and of chromatin modification.

Metastasis-associated factor 1 (MTA1) is another corepressor preferentially binding to a ligand-activated ER [215]. It inhibits the expression of estrogen target genes by competing with coactivators for the binding to the receptor, by recruiting HDAC, and by chromatin modification.

A group of corepressors that might bind both liganded and nonliganded hormone receptors is also known. For example, the NR-binding SET domain containing protein 1 (NSD1) possesses separate domains: one that binds hormone-free receptors TR and RAR (NIDL) and another that binds hormone-bound TR, RXR, ER, and RAR receptors (NIDL) [216].

Interaction of Hormonal Nuclear Receptors with Other Transcription Factors. Natural HREs are located relatively close to TSS or in more distant regulatory elements, and binding sites for other transcription factors are usually located nearby. Such proximity permits interaction between nuclear receptors and these transcription factors, leading either to the suppression of gene activity (as described above) or to its additive or synergistic activation. The binding of nuclear receptors to other transcription factors might also occur in a DNA-binding-independent manner. In fact, the binding of all known nuclear hormone receptors to the transcription factors has been reported; the best known examples are the binding of TR to p53, GR and PR to Oct-1, GR to AP-1 and to NF-κB, PPAR to NF-κB, AP-1, and to STAT [217–221].

2.3.4. Nuclear Hormone Receptors and Chromatin. A nucleosome consists of eight histone molecules (two of each H2A, H2B, H3, and H4). Their N-terminal ends (tails) protrude from the compact nucleosome body. Epigenetic modifications of amino acids forming such tails play a marked role in chromatin organization. Increased acetylation relieves compact chromatin, which results in an exposure of the transcription-factor-binding sites and their increased accessibility leading to transcription activation. On the other hand, deacetylation of histone tails leads to the formation of a compact chromatin. As a result, transcription-factor-binding sites become inaccessible to transactivators, and the gene becomes transcriptionally inactive. Such a mechanism of modification of chromatin structure is utilized by nuclear
hormone receptors, which, as mentioned above, interact with coactivators and corepressors. p160 and p300/CBP coactivators themselves possess HAT activity and form complexes with other HAT proteins, such as p/C/CAF. On the other hand, corepressor proteins recruit class I and class II HDAC proteins to the corepressor complex. The binding of a ligand-activated receptor to HRE initiates the formation of a coactivator complex, which, thanks to the HAT activity, increases histone acetylation and induces local decondensation of chromatin (Figure 5(a)). On the other hand, the binding of a hormone-free receptor to HRE initiates the formation of a corepressor complex, which, thanks to its HDAC activity, induces local condensation of chromatin (Figure 5(b)). Finally, the corepressor complex and its HDAC activity are utilized by the specific corepressor proteins described above, which bind to a hormone-activated receptor and inhibit transcription of the target gene (Figure 5(c)).

3. The Nongenomic Mechanisms of Action of Small-Molecule Hormones

Fast biological effects of hormones, just seconds or minutes after hormone administration, have already been described several dozen years ago. The rapidity of biological response and its independence from transcription and from translation suggested that the genomic mechanism of hormone action is not involved; therefore, this mechanism was called nongenomic or extragenomic. The nongenomic mechanisms of hormone action are multiple, variable, and only partially known (Figure 6).

3.1. Nongenomic Mechanisms of Hormone Action Induced by the Interaction of Hormones with Membrane and Cytoplasmic Receptors. Steroid and nonsteroid small-molecule hormones bind to various proteins localized outside the nucleus and activate transduction pathways leading to a fast biological response. The presence of binding sites in the cell membrane was proved for all major representatives of these hormones; however, in many cases the identity of the binding protein remains unknown. In addition, it is likely that such hormones have more than one type of membrane receptors. In the case of receptors already identified, their mode of action is by and large only partially resolved.

Just next to the cell membrane or directly in it, usually within caveolae (a bubble-like, 50–100 nm invaginations of the cell membrane), proteins identical to the nuclear receptors for glucocorticoids, estrogen, androgen, and vitamin D, have been identified [222–225]. It is then plausible that...
nuclear receptors of other small-molecule hormones are present close to or in the cell membrane. Some small-molecule hormones bind to other than nuclear receptor-like cell membrane proteins. For example, the integrin receptor αVβ3 plays a role of cell membrane receptor for thyroxin (T4) [226]. mPRα, mPRβ, mPRγ, mPRδ, and mPRε cell membrane receptors for progesterone possess seven transmembrane domains (some authors even suggest the presence of eight such domains) and interact with G proteins [227, 228]. The G-protein-interacting cell membrane receptor for steroid-hormone-binding protein (SHBG) binds androgens with higher and estrogens with lower affinity. The prerequisite for signal transduction from the hormone to the cell interior by this receptor is the binding of a hormone-free SHBG first, followed by hormone binding [229, 230]. γ-Aminobutyric acid A (GABA A) receptor serves as the cell membrane receptor for neurosteroids [231].

3.1.1. Nuclear Hormone Receptor Targeting at the Membrane. The best studied is membrane targeting of ER. It is induced by palmitoylation of cysteine 447 [232], a modification increasing protein hydrophobicity and, therefore, facilitating protein association with lipid bilayer. Truncated 46 kDa variant of ERα is preferentially palmitoylated and enriched in the cell membranes [233]; it is suggested that it might be more active than full-length receptor [234]. Another membrane-localized variant of ERα, ERα-36, is also functionally active [235]. Palmitoylation of ER is promoted by HSP27 [236].

Enzymes identified as palmitoylacyltransferases for sex hormone receptors are DHHC-7 and DHHC-21 proteins [237]. A highly conserved 9-amino acid motif (FVCLKSIIL in ERα) that is crucial for palmitoylation and membrane localization has been identified in the ligand-binding domains of ERα, ERβ, PRα, PRβ, GR, and AR [238]. TRα and TRβ possess a motif (LPCEDQIIL) that slightly differs from the one described above, but presumably, it is also involved in the receptor palmitoylation and membrane targeting. Notably, MR, PPARs, and RAR do not have any sequence resembling this motif [238].

Translocation of nuclear hormone receptors to the membrane is also induced in the presence of the respective ligand; this was shown for ERα- and 17β-estradiol [239] and for VDR and 1α,25(OH) 2D3 [240].

In the cell membrane, nuclear hormone receptors interact with caveolae-specific proteins; for example, ERα and AR physically interact with Caveolin-1 [234, 241], while VDR binds to Caveolin-3 [242]. Binding to caveolins is required for membrane localization of the receptor [234]. Furthermore, binding to caveolins allows hormone receptors to initiate fast, specific nongenomic response to hormonal stimulus.

3.1.2. Induction of Transduction Pathways. Upon binding to the cell membrane receptors, small-molecule hormones activate various transduction pathways by a receptor-type-dependent mechanism. By activation of phospholipase C (PLC) and generation of the secondary messenger inositol 1,4,5-trisphosphate (IP3), they might activate the cell membrane and the sarcoplasmic reticulum (the most important Ca 2+ storage) ion channels. Such activation leads to the increase of intracellular concentration of Ca 2+, another secondary messenger crucial for many cellular functions. Ca 2+ activates, among others, RAS/RAF/MEK/ERK kinases, protein kinase C (PKC), and protein kinase A (PKA). As a result, activated kinases phosphorylate and activate numerous cytoplasmic and nuclear proteins, including hormonal receptors, transcription factors and coactivators. This, in turn, modulates various biological processes in the cytoplasm and influences transcription of genes regulated by newly phosphorylated hormone receptors and transcription factors. Cell-membrane-located small-molecule hormone receptors interacting with G proteins might also activate adenylate cyclase, which results in the generation of yet another secondary messenger, cAMP, and in the activation of cAMP-dependent proteins, such as PKA, and of their substrates [243–247]. By nongenomic mechanisms, small-molecule hormones also regulate the activity of ion channels, influencing cross-membrane movement of Na + , H + , Cl – , and of K + [245, 248, 249].

Small-molecule hormones also bind to the proteins present in the cytoplasm; commonly, such proteins are cytoplasmic fractions of nuclear receptors. Upon hormone binding, the receptor interacts with numerous proteins, elements of various signal transduction pathways which, as described above, might be also activated by hormones on a “higher” level, namely, that of a cell membrane receptor. For example, hormone-activated TR, ER, and RAR bind to a p85α subunit of phosphatidylinositol 3 kinase. Activated kinase increases production of IP3 which, in turn, activates the mitogen-activated protein kinase (MAPK) pathway [250–252]. Hormone-activated AR, PR, and ER bind to SH3 or to SH2 subunit of c-SRC tyrosine kinase localized close to the cell membrane. Such binding activates c-SRC which, subsequently, activates MAPK and RAS/RAF/MEK/ERK pathways leading to the phosphorylation of various cytoplasmic and nuclear receptors [253–255].

3.2. Nuclear Hormone Receptor Binding to Calmodulin. Of note is nuclear hormone receptors’ binding to CaM, being an example of cross-talking of hormonal signaling with other signal transduction pathways. Such binding has been proved for ERα (but not for ERβ), AR, and orphan receptor ERRγ, among others [85–87, 256–258]. It results in the increased stability of the receptor due to CaM-dependent protection from degradation [85–87]. CaM facilitates dimerization of ERα in the absence of 17β-estradiol [86]. The binding profoundly affects receptor function: CaM is required for normal transactivation by ERα since its elimination or blockage by antagonists prevents 17β-estradiol from inducing transcriptional activity of this receptor [256, 257]. Similarly, CaM stimulates transcriptional activity of AR (since its antagonist W-7 blocks AR-dependent expression of prostate-specific antigen) and of ERRγ [258, 259].

3.3. Hormone Binding to Nonreceptor Proteins. Small-molecule hormones could also bind to another, nonreceptor type cytoplasmic proteins. For example, 1α,25(OH) 2D3, dehydroepiandrosterone (DHEA), and dexamethasone bind to PKαγ, PKCγ, and PKCe isoforms of PKC, which results in
enzyme activation. In addition, PKCα isoform is also directly activated by aldosterone and by 17β-estradiol, while PKCδ isoform is activated by 17β-estradiol [260, 261].

### 3.4. Small-Molecule Hormones Action in Mitochondria

Small-molecule hormones modulate the function of mitochondria by a number of mechanisms. One of them is based on the action of their nuclear receptors as transcription factors. Each mitochondrion has multiple copies of its own DNA (mtDNA) encoding 37 genes, including genes for 13 proteins involved in oxidative phosphorylation. A shortened isoform of TR (mtTRα1, so-called p43), RXRα (mtRXRα), and PPARγ2 (mtPPARγ2), as well as full-length GR, ERα, and ERβ receptors are present in mitochondria [109, 262–265], where they form dimers such as mtRXRα/p43, mtPPARγ2/p43, GR/GR, and ER/ER or couple with other transcription factors. It has been shown that glucocorticoids, T3 and 17β-estradiol, acting by their mitochondrial receptors bound to mitochondrial HREs, activate the transcription of mtDNA, leading to an increased activity of oxidative phosphorylation.

Another mechanism of small-molecule hormones action in mitochondria is based on their interactions with other proteins. For example, diiodothyronine (T2) binds to the Va subunit of cytochrome c oxidase and activates this enzyme [266]. Adenine nucleotide translocase (ANT) binds all-trans-retinoic acid [267].

In addition, the shortest isoform of TRα1, p28, is bound to the internal mitochondrial membrane [263], where, most likely, it stimulates the function of ANT and of uncoupling proteins (UCPs) [263, 268]. Orphan nuclear receptor Nur77 mediates apoptosis by interaction with Bcl-2 and by induction of cytochrome c release [269].

Small-molecule hormones acting in mitochondria regulate Ca2+ wave activity in this organelle, as shown in the case of estrogens and T3 [270, 271].

Finally, hormonal receptors can directly bind to mitochondrial membranes and modify membrane potential, as shown, for example, for stress-activated GR [272].

### 3.5. Interaction of Hormonal Nuclear Receptors with RNA

It has been shown that RARx molecules present in the cytoplasm can bind mRNA via the C-terminal F domain, which recognizes a specific sequences in the target mRNA. Such a mechanism was described for mRNA encoding neuronal GluR1 protein, a subunit of the glutamnergic receptor. The binding of GluR1 mRNA by a hormone-free receptor results in the inhibition of translation. The binding of all-trans-retinoic acid induces the change of receptor conformation and decreases its affinity for mRNA; as a result the receptor dissociates from mRNA [273].

### 3.6. Direct Interaction of Small-Molecule Hormones with Membranes

A very rapid effects of androgens, progesterone, glucocorticoids, and other steroid hormones, evident just a few seconds after hormone administration, might be a result of a nonspecific, nongenomic mechanism of small-molecule hormones action, based on their interactions with lipid bilayers. Lipophilic steroid hormone molecules could directly bind to membrane phospholipids and, by doing so, modulate their function. This, in turn, influences the

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**Table 2: Selected human pathologies associated with hormone receptors.**

| Receptor | Pathology |
|----------|-----------|
| TR       | Mutation-related generalized and pituitary resistance to thyroid hormone [1–4]; mutations and/or altered expression in various cancers [5–9] |
| RAR      | Translocation in acute promyelocytic leukemia [10]; reduced expression in cancers [11]; altered signaling in neurological and psychiatric diseases [12] |
| VDR      | Mutation-related resistance to 1α,25(OH)₂D₃/hereditary vitamin D resistant rickets [13–15]; polymorphisms in osteoporosis [16]; mutations in alopecia [17]; altered expression and polymorphisms in various cancers [18–20]; altered function in inflammation [21]; altered function in liver pathology [22] |
| PPAR     | Mutations in insulin resistance in nonobese [23]; mutations in familial partial lipodystrophy [23–25]; excessive phosphorylation in insulin resistance and obesity [26]; mutations in cancers, low expression in cancers with poor prognosis [27]; alterations in atherosclerosis, inflammation, and osteoarthritis [28–30] |
| RXR      | Polymorphisms in colorectal cancer and in metabolic diseases [31–33] |
| ER       | Mutations and altered expression in breast cancer [34–36]; altered posttranslational modifications in breast cancer [36, 37]; overexpression in endometriosis [38]; polymorphisms in ovulatory dysfunction [39]; impaired function in metabolic diseases [40] |
| AR       | Mutation-related androgen insensitivity syndrome [41–43]; overexpression, mutations, CAG repeat extension, excessive receptor phosphorylation in prostate cancer [26, 41, 44–46]; CAG repeat extension in spinal and bulbary muscular atrophy [45, 47]; mutations and the AR gene trinucleotide repeat variations in male infertility [48]; mental disorders [41] |
| PR       | Lack of expression in breast cancer [35, 36]; decreased expression in endometriosis [49]; altered expression in testis of infertile men [50] |
| GR       | Mutation-related glucocorticoid resistance [51, 52]; polymorphisms in tissue-specific sensitivity to glucocorticoids and hypersensitivity to glucocorticoids [52]; polymorphisms in depression [53] |
| MR       | Mutations in mineralocorticoid resistance syndrome (pseudohypoaldosteronism type 1) [54]; polymorphisms in depression [53]; mutation in severe hypertension [55] |
function of membrane proteins such as the calcium pump and other channel proteins, leading to an immediate transport modification of various ions. Nonspecific binding of steroid hormones to a mitochondrial membrane might increase proton leak [274, 275].

4. Human Pathologies Associated with Receptor Abnormalities

Medical conditions associated with out-of-range level of small-molecule hormones are known for decades, relatively common, and have been exhaustively described in numerous handbooks and articles. In contrast, much less is known about diseases initiated by abnormalities of the receptor. They are uncommon, with a wide range of signs and symptoms of variable severity (related to both the type and site of genetic error within the receptor-encoding gene or related genes) that might mimic signs and symptoms of other diseases (e.g., resistance to thyroid hormone might be erroneously diagnosed as hyperthyroidism). Detailed description of these diseases exceeds the scope of this paper; however, in Table 2 the reader can find a comprehensive summary and references to the review and original articles regarding selected human hormone-receptor-related pathologies.

Hormone-receptor-related diseases constitute an important diagnostic challenge. Among them, a monogenic diseases arising due to mutation are the easiest to diagnose, provided that a candidate gene is identified and its sequencing shows mutation. It is much more difficult, though, to evaluate the influence of altered expression or function (e.g., due to the abnormal posttranslational modifications) of the receptor on the phenotype, especially of multifactorial diseases such as obesity, insulin resistance, atherosclerosis, cardiovascular disease, cancer, neurodegeneration, and so forth. The Diagnostic problems are the reasons why hormone receptor dysfunctions commonly remain undiagnosed and untreated. However, the importance of such dysfunctions in pathophysiology of both rare and common diseases fully justifies the efforts to elucidate the molecular mechanisms of action of these receptors. Importantly, identification of these mechanisms is crucial for designing new targeted therapeutic strategies.

5. Conclusion

Small-molecule hormones, usually of quite simple chemical structure, have an enormously wide range of biological functions. The effects of their action are due to their interaction with various receptors, which, by further interaction with other proteins or with DNA, activate various signal transduction pathways or regulate the activity of numerous target genes. Even though our knowledge regarding these nongenomic and genomic mechanisms is already impressive, a lot of information regarding, first of all, their interdependence still awaits elucidation.

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