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Review

Activation of steroid hormone receptors: Shed light on the *in silico* evaluation of endocrine disrupting chemicals

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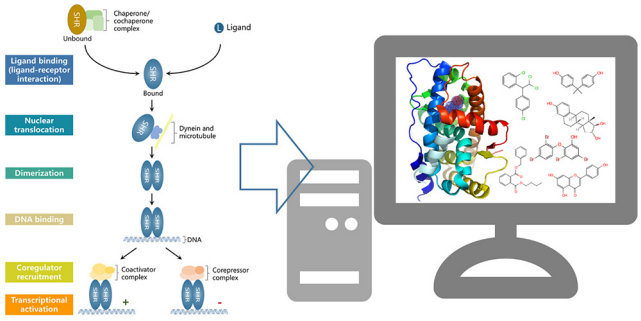
HIGHLIGHTS

- Published crystal structures of SHRs are used to identify the mechanisms of SHR activation.
- Binding and unbinding processes are used to evaluate ligand-receptor interactions.
- Nuclear translocation is important to the AR, GR and MR, while dimerization is important to the ER.
- H12 can be positioned in 3 regions, which result in steric hindrance, AF2 inhibition and competitive binding.
- The mechanisms of action of SHR activation are helpful for the computational evaluation of EDCs.

GRAPHICAL ABSTRACT



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ABSTRACT

Endocrine disrupting chemicals (EDCs) are of great concern given their potential influence on the endocrine system. *In silico* methods for the evaluation of EDCs have been widely recognized. However, subcellular molecular mechanisms of action, such as ligand-receptor interactions, receptor conformational switch and protein-protein interactions, are needed for the development of mechanism-based *in silico* models. Here, molecular mechanisms of action for steroid hormone receptors (SHRs), the important targets of EDCs, are systematically reviewed. Ligand binding and ligand-receptor interactions are required for SHR activation, and facilitate the nuclear translocation and the dimerization of SHRs. Coregulator recruitment results from conformational switch of SHR, which regulates the transcription and results in either an agonistic or an antagonistic effect. EDCs potentially interfere with SHRs by influencing ligand-receptor interactions, nuclear translocation, dimerization and coregulator recruitment. These new findings shed light on the development of mechanism-based computational models for the evaluation of EDCs.

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Contents

1. Introduction

Endocrine disrupting chemicals (EDCs) are chemicals that interfere with any aspect of hormone action (Zoeller et al., 2012). Many natural and synthetic chemicals are reported as EDCs, such as bisphenol A (BPA) (Rogers et al., 2013), dioxins (Bruner-Tran et al., 2017), polybrominated diphenyl ethers (PBDEs) (Erkin-Cakmak et al., 2015), polychlorinated biphenyls (PCBs) (Fiandanese et al., 2016), perfluorinated chemicals (Tijani et al., 2016) and organochlorine and organophosphate pesticides (Shapiro et al., 2016), have been detected in our surrounding environment (Annamalai, Jayshree; Namasivayan, 2015; Padhye et al., 2014), diet (Mezcua et al., 2012) and body (Ballesteros et al., 2014; Xue et al., 2015). EDC exposure is the potential cause of adverse health effects, including reproductive dysfunctions (Dickerson and Gore, 2007), birth defects (Fernandez et al., 2007), prostate and breast cancers (Soto and Sonnenschein, 2010), cardiopulmonary disease (Melzer et al., 2012), obesity, diabetes (Legler et al., 2015) and neurobehavioral and learning dysfunctions (Mustieles et al., 2015). The annual cost of EDC exposure is approximately $209 billion in the European Union, roughly 1.23% of the gross domestic product (Trasande et al., 2015). Therefore, EDCs are being paid more attention.

Steroid hormone receptors (SHRs), such as estrogen receptor (ER, including its two isotypes, ERα and ERβ), androgen receptor (AR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and progesterone receptor (PR) (Beato and Klug, 2000), are nuclear receptors. They are important targets for EDCs. SHRs are ligand-dependent transcription factors whose activities are highly dependent on ligand binding (Fig. 1A). In the absence of ligand, SHRs are predominantly monomeric and bind to chaperones/cochaperones complexes to maintain stabilized in the cytoplasm. To dissociate from chaperones/cochaperones and translocate to the nucleus, the AR, GR and MR must be bound by ligands while the ER and PR are able to translocate into the nucleus in the absence of ligand (Dull et al., 2010; Kil and Kalinec, 2013). Once in the nucleus, the SHRs form dimers, bind to specific genomic DNA response elements and recruit coregulators. The SHRs then bind other transcription factors to form transcription regulatory complexes to activate or repress transcription. Although the sequence of nuclear translocation and dimerization is still ambiguous, the two processes are essential for the activation of the SHRs (Marcelli et al., 2006; van Royen et al., 2012; Zhan et al., 2017). An agonist induces an active conformation of the SHR that recruits coactivators and activates transcription. Contrarily, an antagonist induces an inactive conformation of the SHR that recruits corepressors and represses transcription. SHRs consist of four characteristic domains, namely, the N-terminal domain (NTD), the DNA-binding domain (DBD), the hinge region and the C-terminal ligand-binding domain (LBD) (Fig. 1B). Two functional regions, the activation function region 1 (AF1) and AF2, are embedded in the four domains and regulate SHR activity. AF1 and AF2 are located in the NTD and the LBD, respectively (Weikum et al., 2017). Different domains are responsible for different functions. Coregulator recruitment and the subsequent transactivation are dependent on the AF1 and the AF2. DNA binding predominantly occurs in the DBD. Nuclear localization is dependent on the hinge domain and the LBD. All four domains contribute to the dimerization of the SHR. Ligand binding and ligand-receptor interactions happen mainly in the LBD. Therefore, EDC binding affects the ligand-receptor interaction, nuclear translocation, dimerization and coregulator recruitment, thus interferes with the action of SHRs.

In vitro and *in vivo* studies have screened and evaluated EDCs targeting SHRs. For example, the United States Environmental Protection Agency (US EPA) initiated ToxCast, Tox21 and the Endocrine Disruptor Screening Program (EDSP), in which more than 8000 chemicals were screened using high throughput *in vitro* assays to detect the potential endocrine disrupting effects (Table 1). However, it is impossible to cover a range of more than 135 million existing chemicals (https://support.cas.org/) using *in vitro* or *in vivo* assays. Computational models using (quantitative) structure-activity relationship ((Q)SAR) (Devillers et al., 2006; Zhang et al., 2013), molecular docking (Li et al., 2012), molecular dynamics (MD) simulations (Wang et al., 2013b) and other *in silico* methods have the potential to evaluate EDCs based on their mechanisms of action. Although the EDSP aims to develop computational models to allow quick and cost-effective evaluation of EDCs,