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Summary:

Abstract

The impact of endocrine disruptors (EDs), compounds disturbing the normal action of hormones, represents a major field of toxicological research, in particular through the interference with steroid hormones and their nuclear receptors. By contrast, G-protein coupled receptors (GPCRs) have been a major focus of pharmacological research and drug-development, but have received limited attention in toxicology as potential targets of EDs. In this review we discuss the potential importance of GPCRs in the mode of action of EDs, using the recently observed interaction between polycyclic aromatic hydrocarbons (PAHs) and β-adrenergic receptors as an example. This ability to disturb adrenoceptor function represent a novel mode of action (MOA) for hormone disruption by EDs which may affect both metabolic processes and immune responses. The outcome may be of relevance to development or exacerbation of multifactorial non-communicable diseases (NCDs).

Introduction

Throughout life, people are widely exposed to environmental contaminants found in various consumer products, such as foods and personal care products, and from polluted air and water. Numerous biological and epidemiological studies have demonstrated that anthropogenic chemicals could induce or exacerbate effects deleterious to human health, including developmental, reproductive, neurological, and immune outcomes. Thus, chemical exposure constitutes a major environmental risk factor associated with the increased incidence and prevalence of non-communicable diseases (NCDs) including asthma and allergies, cancers, neurological disorders and metabolic syndromes such as diabetes and obesity [1].

Endocrine disruptors (EDs), compounds interfering with the hormonal system, have gained considerable attention and concern within toxicology and environmental health. The molecular mode of action of EDs has been most extensively studied for the more traditional hormone disruptors, triggering effects through nuclear receptors (i.e. steroid hormone disruptors). Nevertheless, it seems unlikely that disturbance of steroid receptors could be the only pathways responsible for the pleiotropic effects of EDs. Several arguments support this assertion:

i. A number of studies demonstrate a non-monotonic dose-response effects on the endocrine system. These kinds of observations could be explained by the addition of counteracting monotonic dose responses. Each monotonic dose response being related to a precise receptor/biological pathway [2].

ii. Some effects mediated by EDs are independent of steroid receptors and are observed in cell lines that do not express steroid receptor [1].

iii. Several EDs, by their chemical structures, appear as privileged binders, with the ability of interacting with numerous receptor such as: steroid receptors, aryl hydrocarbon receptor, peroxisome proliferator-activated receptor, constitutive androstane receptor, Pregnane X receptor [3].

iv. The occurrence of rapid effects of some EDs is kinetically compatible with membrane receptors signaling, such as G protein coupled receptor (GPCR) machinery. Thus membrane receptors could be unsuspected targets for EDs, as already demonstrated for B(a)P and the beta2-adrenergic receptor (β_2AR). Like B(a)P, some EDs can modulate the concentration of intracytosolic cAMP or Ca^{2+} (both acting as second messengers for GPCR) via G protein-dependent mechanisms, or at least without the involvement of the receptors conventionally associated with their toxicity [2-8].

GPCRs as potential toxicological target

Interactions between manmade chemical and cell membrane components has received relatively limited attention in toxicology, considering the significant importance of cell surface receptors and ion channels as therapeutic targets in pharmacology and medicine. One of the most important groups of molecules which transfer signals across the plasma membrane are the GPCRs. GPCRs constitute a large family of 7-transmembrane domain receptors distributed across nearly all of the body's organs and tissues, including the cardiovascular, immune, nervous systems and the overall endocrine systems. This superfamily of cell surface proteins acts as central molecular activators and integrators in major human biological systems. Their biological actions include modulation of neuronal firing, regulation of ion transport across the plasma membrane and within intracellular organelles, regulation of homeostasis (e.g. water balance), cell growth and differentiation, and modification of cell morphology [9]. Due to their central role in all physiological systems, GPCRs constitute a major area of research in pharmacology, and perturbations in their activity can result in a multitude of diseases including asthma, cancer, neurological disorders, obesity and several other health outcomes [10-12]. Their medical importance is underscored by the fact that they are the targets of approximately 40% of all modern medicinal drugs. A number of GPCR-ligands contain aromatic structures, making them potential targets of aromatic pollutants. Moreover, their most important regulatory sites are displayed at or near the extracellular surface making them readily available for circulating compounds.

Complexity of GPCR regulation

GPCR activation/inactivation does not operate in a simple two-state (on/off) model. Varying degree of ligand efficacy and multiple receptor configurations enable a continuum of different signaling outcomes from GPCR-ligation [9]. Ligands of GPCRs have been classified as i) full or partial (positive) agonists with various levels of signaling activation, ii) biased agonists which produce activation of some but not all available pathways, iii) (neutral) antagonists that simply block signaling through the receptor (but without any effects in absence of a competing agonist) and iv) inverse agonists which suppress receptor signaling beyond base-line levels (Fig 1). In addition, GPCRs are coupled to multiple signaling pathways including G proteins dependent and/or independent pathways (*i.e.* stimulation or inhibition of cAMP production, stimulation of phospholipase C with subsequent mobilization of intracellular Ca^{2+}, activation of plasma membrane proton flux, activation of β-arrestin pathways, etc.) [9]. The ability of different ligands to induce all or some of these pathways can vary considerably [13]. Thus, for any compound identified to bind a GPCR, interpreting the outcome of such interactions may not be straightforward. Adding further complexity to the system, GPCR activation/inactivation is not limited to traditional (orthosteric) interactions at the ligand-binding site, but also involves allosteric activation/modulation through interactions with other parts of the receptor structure[9]. This means that interference with physiological ligands or potential ligands such as EDs may not be restricted to the ligand-binding site of GPCR, which theoretically increases the potential range of compounds that may disturb the GPCR system.

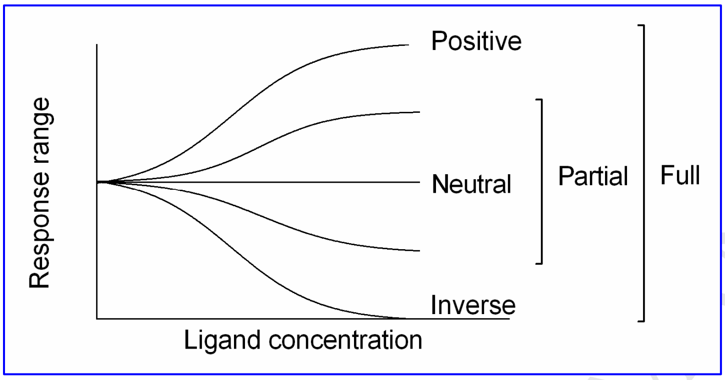

Fig. 1: Directional effects of GPCR activation. GPCR ligands may act as positive/inverse agonists or as neutral antagonists not affecting basal receptor activity. Moreover, ability to stimulate responses may vary from full to partial agonism.

Interference with β-adrenoceptor signaling – a novel mode of hormone disruption.

β-adrenoceptors are a subgroup of the adrenergic receptors (ARs), a family of GPCRs that transmit signaling from the catecholamine hormones epinephrine and norepinephrine (adrenaline and noradrenaline; produced by the adrenal medulla and sympathetic nerve termini) and act as central regulators of the body's reaction to stress. They are central in control of cardiopulmonary function, immune responses and homeostasis, and are among the main drug targets for treatment of obstructive pulmonary diseases and cardiovascular disorders. The β-adrenergic system contains three receptor subtypes, β_1, β_2, and β_3. β_1 and β_2 are distributed at varying concentrations in the lung and heart, as well as in peripheral tissue throughout the body, while β_3 is mainly expressed in adipose tissue where it regulates lipolysis. Recent studies have shown that polycyclic aromatic hydrocarbons (PAHs), which are widely distributed environmental contaminants from combustion sources such as automobile exhaust, cigarette smoke, grilled foods and industrial waste by-products, could interfere with β-adrenoceptor signaling. Indeed, it was demonstrated that a mixture of PAHs representative of levels in outdoor air impaired function and expression of the β_2AR [14, 15]. Even if the majority of cellular effects of PAHs are attributed to activation of aryl hydrocarbon receptor (AhR) and subsequent metabolism by cytochromes P450 (CYP)-enzymes [16], the prototypical carcinogenic PAH benzo[*a*]pyrene (B[*a*]P) was shown to interact directly with the ligand binding pocket of the β_2AR at low concentrations (Kd~ 10 nM). This led to a subsequent increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) in endothelial cells and HEK293 cells through a pathway involving activation of G-proteins and cyclic AMP (cAMP) [8]. Although the toxicological implications remain unclear, changes in $[Ca^{2+}]_i$ play a key role in regulation of most endothelial functions. Interference with Ca^{2+} signaling could therefore lead to endothelial dysfunction [17]. Recent findings also indicate that B[*a*]P may promote β_2AR-desensitization by stimulating receptor endocytosis, thus attenuating responses induced by epinephrine [18]. Furthermore, a study on adipocytes suggests that B[*a*]P disturbs epinephrine signaling through all the three β-adrenoceptors [19], underscoring that adrenoceptor disruption is not limited to interference of β_2AR function. Notably, epinephrine and norepinephrine reacts with 9 different subtypes of the adrenergic receptor family ($\alpha_{1A/B/D}$, $\alpha_{2A/B/C}$, β_1, β_2 and β_3). Thus, effects could potentially extend to the α-adrenoceptor family as well.

Potential metabolic effects from interference with β_2AR-function

There is an increasing concern that environmental contaminants affect energy metabolism and metabolic disorders such as obesity and diabetes. Recent epidemics of metabolic diseases cannot be attributed only to genetic background, lack of physical exercise and junk food or ageing populations. It is currently accepted that exposure to EDs may be implicated in the growing incidence of some metabolic diseases such as diabetes, obesity or dyslipidaemia [20]. Energy metabolism homeostasis involves controls of opposing metabolic pathways such as lipolysis and lipogenesis, glycolysis and gluconeogenesis, or fatty acid oxidation and synthesis. Most of these pathways are linked directly or indirectly to GPCRs and numerous GPCRs possess, as ligands, energy substrates (such as fatty acids and sucrose) or metabolic intermediates (such as acetate, lactate or ketone bodies) [21, 22]. Activation of the adrenergic system plays a central role in the regulation of metabolism. As reviewed elsewhere, activation of adrenergic receptors increase lipolysis in adipocytes and release of fatty acids in plasma, increase gluconeogenesis in the liver, and moderately inhibits insulin release by the pancreas [23]. Thus, disturbance of adrenoceptor function would be expected to affect metabolic function. In line with this, B[*a*]P has also been reported to impair epinephrine-induced lipolysis in adipocytes through interference with β-adrenoceptors, and this effect was associated with weight gain in mice [19]. B(a)P has also been found to induce cellular metabolic reprogramming, associated to the increase of ATP Inhibitory Factor 1 expression which might rely on β_2AR activation [24, 25].

However, the toxicological action of B[*a*]P has traditionally been attributed to interaction with the aryl hydrocarbon receptor (AhR), with subsequent activation of CYP1 enzymes (CYP1A1/-1A2/-1B1) and metabolic activation of B[*a*]P leading to formation of reactive metabolites and oxidative stress [26]. Of notice, the B[*a*]P-induced $[Ca^{2+}]_i$ through β_2AR appear important for CYP-activation through AhR [8]. Thus, interference with β_2AR may also affect the bioactivation of B[*a*]P and other toxicants metabolized by CYP1A1/1B1.

Role of β_2AR in the regulation of inflammation and immune responses

Throughout the past decades it has become clear that β_2AR also modulates immune responses and inflammation, amongst others through interaction with the archetypical pro-inflammatory transcription factor Nuclear Factor-κB (NF-κB). As inflammatory responses are considered central to development of metabolic disorders [27], this represent another mechanism through which disturbance of adrenoceptor signaling by EDs potentially could affect metabolic function. β_2AR appear to interact with NF-κB signaling at multiple levels with bidirectional effects on NF-κB-driven gene expression. While the majority of studies suggest an anti-inflammatory function of β_2AR, pro-inflammatory effects have also been reported [28, 29]. The β_2AR agonists salbutamol and salmeterol have been found to enhance CXCL8 and interleukin-6 (IL-6) responses by IL-1β or virus infections in BEAS-2B cells and primary human bronchial epithelial cells [30, 31]. However, salbutamol and salmeterol had no effect on CXCL8 or IL-6 responses alone, suggesting that β2AR-signaling alone may be insufficient for activation of cytokine/chemokine responses. CXCL8 responses in BEAS-2B cells exposed to the 1-nitropyrene, a typical PAH from diesel exhaust, was attenuated by β_2AR knock-down or pretreatment with the β_2AR-selective inhibitor ICI 118551 [32]. Moreover, cigarette smoke and cigarette smoke extracts were reported to induce transcription and secretion of MUC5A in bronchial epithelial cells (NCI-H292) through a pathway involving β_2AR, β-arrestin2, and the MAPKs ERK1/2 and p38 [33]. β_2AR is also the predominant adrenoceptor expressed by immune cells and regulates the activity of both T and B lymphocytes [34, 35]. This further underscores the potential for immunological effects if anthropogenic chemicals interfere with epinephrine or norepinephrine signaling.

Concluding remarks

Recent studies have revealed a novel molecular mechanism of PAH toxicity, interference with β-adrenoceptor function. Reported effects include interaction with the ligand binding site, interference with receptor signaling, receptor downregulation/desensitization and disturbance of effects from natural ligands (epinephrine) and pharmacological β-agonists. The β_2AR is extensively expressed in different system (respiratory, nervous, cardiovascular, inflammation and immune systems), and promote various physiological functions (bronchodilation, regulation of vasodilation and cardiac muscle contractility, regulation of activities of both T and B lymphocytes, homeostatic and neuroprotective functions, lipolysis regulation) [28, 29, 34-40]. Hence, the observation that B[*a*]P at low concentrations can bind and stimulate β_2AR signaling and attenuate effects from epinephrine [19, 8, 18] is potentially of considerable toxicological importance. As shown in Table 1, interference with GPCRs is not restricted to PAHs and β-adrenoceptors, but other GPCR-targets affected by other EDs are emerging. Thus, GPCR disruption could be a central mechanism contributing in several NCDs associated with exposure to anthropogenic chemicals. This underscores the need of a wider assessment of disturbance of GPCR-function by environmental chemicals. This evaluation must notabely include energetic metabolism. Indeed, GPCRs are strongly associated with the control of secretions of metabolic hormones and with the regulation of the metabolic activity of cells. Moreover, most of these receptors appear to be involved in the pathophysiology of metabolic diseases. Despite literature indicating that energetic metabolism and metabolic reprogramming play a role in the cell responses induced by environmental contaminants [20-21], influence on energetic metabolism of many environmental contaminants remain to be investigated.

Table 1: Examples of GPCRs targeted by environmental contaminants.

	targeted GPCR	**level of effect**	**References**
TCDD	GPCR signaling pathway (ADRB2…)		[41]
4-nonylphenol	alpha2A-adrenergic	binding (suspected)	[42]
	D2 dopaminergic	mRNA level	[43]
	D1A dopaminergic	mRNA level	
	adenosine A3	binding (suspected)	[42]
	5-HT2C (serotonin)	binding (suspected)	[42]
Bisphenol A	D3 dopaminergic	protein level	[44]
	5-HT6 (serotonin)	binding (suspected)	[42]
phthlates	CB1 cannabinoid	binding	[45]
	D2 dopaminergic	mRNA level	[43]
B(a)P	various GPCRs	mRNA level	[46]
	D2L dopaminergic	binding (suspected)	[42]
	Beta2-adrenergic	mRNA and protein level ; binding	[8]
	Beta1/-2/-3-adrenergic		[19]
PAH mixtures	Beta2-adrenergic	mRNA level, impaired epinephrine signaling	[14, 15]
acetaminophene	CB1 cannabinoid	binding (suspected, indirect effect)	[47]
Diesel exhaust particles	PAR-2	activation of $G_{i/o}$-dependent signaling	[48]
1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene (p,p'-DDT)	follitropin receptor (FSHR)	positive allosteric modulator	[49]

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