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Invited Review Article

Xenobiotics and the Glucocorticoid Receptor

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ABSTRACT

Glucocorticoid Receptor (GR) is present in virtually every human cell type. Representing a nuclear receptor superfamily, GR has several different isoforms essentially acting as ligand-dependent transcription factors, regulating glucocorticoid-responsive gene expression in both a positive and a negative manner. Although the natural ligand of the Glucocorticoid Receptor, glucocorticoids (GC) represent only some of the multiple ligands for GR. Xenobiotics, ubiquitous in the environment, bind to GR and are also capable of activating or repressing GR gene expression, thereby modulating GR cell and tissue-specific downstream effects in a multitude of ways that include responses to inflammatory, allergic, metabolic, neoplastic and autoimmune processes. Many xenobiotics, if inadequately metabolized by xenobiotic metabolizing enzymes and not wholly eliminated, could have deleterious toxic effects with potentially lethal consequences. This review examines GR, the genomic and non-genomic actions of natural and synthetic GC and the body's handling of xenobiotic compounds, before reviewing what is presently known about GR's interactions with many of the more commonly encountered and some of the less well known GR-associated xenobiotics. GR promiscuity and crosstalk with other signaling pathways is discussed, alongside novel roles for GR that include mood disorder and addiction. A knowledge of GR interactions with xenobiotics is increasingly relevant when considering aging populations and the related prevalence of neoplastic disease, together with growing concerns around human exposure to mixtures of chemicals in the environment. Furthermore, escalating rates of obesity, Type 2 diabetes; autoimmune, allergy, addiction and mood disorder-related pathologies, require novel targeted interventions and GR appears a promising pharmacological candidate.

Contents

Abbreviations: GC, Glucocorticoids; GR, Glucocorticoid Receptor; NR, Nuclear receptor; PXR, Pregnane X receptor; CAR, Constituitive androstane receptor; SCN, Supra-chiasmic nucleus; CBG, Corticosteroid binding globulin; HSD, Hydroxysteroid dehydrogenase; MR, Minerocorticoid receptor; GRE, Glucocorticoid response elements; PR, Progesterone receptor; MAPK, Mitogen activated protein kinase; SGK1, Serum glucocorticoid protein kinase 1; GILZ, Gene encoding glucocorticoid-induced lucine zipper; CRH, Corticotrophic releasing hormone; ACTH, Adrenocorticotrophic hormone; PEPCK, Phosphoenolpyruvate carboxykinase; NF-κB, Nuclear factor kappa B; FAS, Fatty acid synthase; GPAT, Glycerol-3-phosphate O acetyl transferase; ACC, Acetyl-coenzyme A; HAD, Histone deacetylase; SLP1, Secretory leukoprotease inhibitor; TNFα, Tumor necrosis factor alpha; GSK-3, Glycogen synthase kinase-3; COX, Cyclooxygenase; GM-CSF, Granulocyte macrophage-colony stimulating factor; PPAR, Peroxisome proliferator-activated receptor; PGE2, Prostaglandin E2; TCR, T cell receptor; HPA, Hypothalamic pituitary adrenal (axis); CNS, Central Nervous System; TH, Tyrosine hydroxylase; MHPG, 3-methoxy-4-hydroxyphenylethylen glycol; AEA, endocannabinoids anadamide AEA; 2-AG, 2-arachidonoylglycerol; PKA, Protein kinase A; JNK, c-Jun N-terminal kinase 1; NO, Nitric oxide; BPA, Bisphenol A; HHPA, Hippocampal hypothalamic pituitary adrenal (axis); PSD, Post traumatic stress disorder; ER, Estrogen receptor; BMP, Bone morphogenic protein; NcoA2, Nuclear coactivator 2; SERM, Selective Estrogen Receptor Modulators; TZD, thiazolidinedione; iNOS, Inducible nitric oxide synthase; BADGE, Bisphenol A diglycidyl ether; TCCD, 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (dioxin); FABP, Macrophage fatty acid binding protein; AhR, Aryl hydrocarbon receptor; XRE, Xenobiotic responsive element; FPP, farnesyl pyrophosphate; EDC, endocrine disrupting chemicals; C/EBP, CCAAT enhancer-binding proteins; DPB, di (n-butyl) phthalate; AR, Androgen receptor; PFOS, Perfluorooctane sulfonate; BP, Blood pressure; EPA, Environmental Protection Agency.

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1. Introduction

The chemicals to which an organism is exposed and which are extrinsic to the metabolism of that organism are referred to as xenobiotics (Croom, 2012). Xenobiotics that humans are exposed to include a vast range of possibilities; occupational chemicals, pesticides, illicit, over the counter and prescription drugs, environmental contaminants, deployment-related chemicals, exogenous chemicals generated by other organisms, and the list continues (Croom, 2012). Xenobiotics are eliminated via the kidneys or gastrointestinal tract having undergone no to extensive metabolism. Xenobiotic metabolizing enzymes are capable of metabolizing several different classes of xenobiotics so that the same enzyme isoform that successfully metabolizes pharmaceuticals can be just as effective in the metabolism of pesticides (e.g. the Cytochrome P450 enzyme sub-type CYP3A4). Without the ability for metabolic breakdown, xenobiotics would accumulate in the human body culminating in potentially lethal toxicity (Croom, 2012).

Xenobiotic metabolizing enzymes are classified as being phase I, phase II and transporter enzymes, with phase I enzymes metabolizing lipophyllic xenobiotics to make them more polar so that the phase II enzymes can perform the necessary conjugation reactions that afford elimination. Although the phase II enzymes more commonly interact with the product of phase I enzyme metabolism, they can also interact directly with the more polar xenobiotics, eventually eliminating metabolites from the body using both passive and active transport mechanisms. In effect, most xenobiotics are cleared using multiple enzymes and pathways but for a great deal of xenobiotics, the exact enzyme and pathways utilized are yet to be determined. Both developmental age and genetics have a role in determining susceptibility to the effects of particular xenobiotics and just which metabolic reactions dominate in a given individual will involve relative chemical dose exposure alongside enzyme affinity and enzyme and cofactor availability (Croom, 2012).

It is significant regulation, at gene expression level, by members of the nuclear receptor (NR) family of ligand-modulated transcription factors (Wallace and Redinbo, 2013) that enables the above-mentioned catalytic systems to perform processes such as oxidation, conjugation and transport of potentially deleterious xenobiotic and endobiotic compounds. NRs activated by a variety of endo- and exogenous chemicals are also required for the induction and suppression of drug-metabolism pathways and are closely involved in the pathogenesis of human diseases (e.g. cancer, diabetes, inflammatory disease, metabolic disease and liver disease). Glucocorticoid Receptors (GR), although not sharing the degree of promiscuous xenobiotic binding activity seen with the NR, pregnane X receptor (PXR) and to a lesser extent the constitutive androstane receptor (CAR), nevertheless play important roles in the regulation of metabolic gene expression involving xenobiotics.

This paper aims to review the Glucocorticoid Receptor NR family in the context of the biological impact of xenobiotics acting through these receptors.

2. Background on glucocorticoids

Glucocorticoids (GC), the natural ligand of the Glucocorticoid Receptor (GR) are cholesterol-derived lipophilic steroid hormones produced by the adrenal glands. Endogenously-produced glucocorticoids include cortisone (the predominant form in humans), cortisol and corticosterone (rodents) (Biddie et al., 2012). Hormonal levels of GC follow a circadian rhythm with highest serum cortisone levels occurring in the morning shortly after waking and lowest around midnight (Chan and Debono, 2010). Regulation of hormone secretion is achieved by way of negative feedback involving the hypothalamic-pituitary-adrenal (HPA) axis. Essentially, the HPA axis receives input from circadian oscillators (pacemaker cells) situated in the supra-chiasmic nucleus (SCN) of the hypothalamus. The pacemaker controls circadian release of corticotrophin-releasing hormone (CRH) from the cells of the paraventricular nucleus in the same structure. CRH, also secreted in response to physical and emotional stressors, brings about the release of adrenocorticotrophic hormone (ACTH) from the pituitary corticotrophs, which in turn stimulates the release of adrenal cortisol. Rising serum cortisol levels serve to inhibit further CRH and ACTH release in a classical feedback loop (Chan and Debono, 2010). Evidence also exists for pacemaker cells, located in peripheral tissues, as having a role in supporting circadian rhythm (Balsalobre et al., 2000).

In humans, the availability of endogenous GC is also regulated by serum levels of corticosteroid-binding globulin (CBG), and by tissue levels of 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes that catalyze the interconversion of cortisol and cortisone (van Uum et al., 1998). Endogenous production of GC is critical in maintaining both basal and stress-related homeostasis through the regulation of growth, development, metabolism, reproduction, blood pressure and circulation, the immune and inflammatory responses, water and electrolyte homeostasis, cognition and behaviour (Nicolaides et al., 2010; Nicolaides et al., 2015).

Since the late 1940s, synthetic GC (e.g. prednisone, prednisolone, dexamethasone) have been used extensively in the treatment of chronic inflammatory conditions such as rheumatoid arthritis and asthma, and for their immunosuppressant action in preventing organ rejection post transplantation. Corticosteroids are also used to hasten maturation of the fetal lung, thus decreasing prematurity-associated mortality and morbidity from respiratory causes (Liggins and Howie, 1972) (Crowley, 1995; Kadmiel and Cidlowski, 2013; Bolt et al., 2001). Synthetic GC have been prescribed for many years in palliative care settings for a range of reasons, although such non-specific use has been questioned (Denton and Shaw, 2014). Finally, GC exhibit anti-proliferative, pro-apoptotic and anti-angiogenic properties (Almari and Melemedjian, 2002; Nauck et al., 1998). These drugs thus represent a powerful arsenal in the treatment of multiple conditions sharing an inflammatory, allergic, neoplastic or autoimmune basis. It is well recognized, however, that long-term administration of synthetic GC comes at a cost. Synthetic glucocorticoids, unlike natural glucocorticoids may not be susceptible to inactivation by 11β-HSD (e.g. dexamethasone), nor be bound by CBG. Thus, potency and metabolic clearance of the synthetic steroid can differ from that of the endogenous ligand (Kadmiel and Cidlowski, 2013), perhaps contributing to the multiplicity of adverse effects associated with prolonged and excessive exposure to exogenous GC. Undesirable effects may manifest in many body systems and include osteoporosis, muscle wasting, skin atrophy, delayed wound healing, impaired reproductive function, glaucoma, Cushing's disease (presenting as central adiposity, hyperglycaemia, hyperlipidaemia and hepatic steatosis), insulin resistance, overt diabetes, cardiovascular disease and immunosuppression (Kadmiel and Cidlowski, 2013; van Raalte et al., 2009). Of relevance to this review are also the systemic effects of hypoadrenalism whereby insufficient adrenal glucocorticoid, mineralocorticoid and sex hormone secretion is manifested in symptoms of profound lethargy, ACTH-associated skin pigmentation, hypotension, hypoglycaemia, weight loss and the inability to respond