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Glucocorticoid Induced Immune Modulations Molecular Biology to Clinical Research

Dean Sittig*

Department of Medical Informatics, Northwest Permanente, Portland, OR, USA

Abstract

For more than 70 years, glucocorticoids have been used to treat autoimmune and inflammatory diseases because of their potent anti-inflammatory and immune-suppressive properties. The severity of their side effects, which include osteoporosis, muscle wasting, hyperglycaemia, and hypertension, as well as the occurrence of resistance to glucocorticoid therapy, limit their use. An overview of our current understanding of the mechanisms underlying glucocorticoid treatments therapeutic and side effects, as well as the decreased sensitivity observed in resistant patients, is provided in this Special Issue. In addition, research that aims to either prevent or treat glucocorticoid resistance or to develop novel glucocorticoid therapies with fewer side effects is highlighted. The calming impacts of glucocorticoids are interceded by an intracellular receptor, the glucocorticoid receptor (GR). A wealth of information regarding which cells are the primary targets of the therapeutic effects of glucocorticoids has been provided by research conducted over the course of the past two decades using cell type-specific GR knockout mice in conjunction with models of infectious, autoimmune, and inflammatory diseases. This appears to be the case for both the effects of the endogenous glucocorticoid corticosterone on immune function and the therapeutic effects of glucocorticoid drugs on the disease. When all of these studies are taken into account, it becomes clear that glucocorticoids may target a variety of immune system cells, including innate lymphoid cells, T- and B-cells, myeloid cells (granulocytes, macrophages, and dendritic cells), as well as non-immune cells like epithelial and stromal cells.

Keyword: Glucocorticoid • Granulocytes • Dendritic cells

Introduction

Intriguingly, the primary target cell that mediates glucocorticoid's anti-inflammatory effect varies significantly between disease models. T cells were found to be necessary for the glucocorticoid effects in antigen-induced arthritis, graft-versus-host disease neuroinflammation and inflammatory bowel disease models. In contrast, T cells were found not to be involved in glucocorticoid action in other arthritis models (induced by collagen and serum transfer) and contact dermatitis models. Myeloid cells appeared to be important in this second model, and they were also necessary in a model of acute lung injury. In a model of allergic asthma, it was demonstrated that stromal cells were the primary target and that no immune system cells appeared to be involved in the glucocorticoid's action. In the collagen- and serum-transfer induced arthritis models, glucocorticoid effects were mediated by a similar cell type that strongly interacts with macrophages. These steroids bind the GR in the various cell types that are targeted by glucocorticoids. The GR then becomes activated and functions as a transcription factor, regulating the expression of numerous genes. There are a number of ways that the GR affects these genes' transcription rates, some of which require the receptor to dimerize. It can transactivate genes by directly binding to DNA glucocorticoid response elements (GREs) as a homodimer complex. It can also bind to negative GREs and stop gene transcription, or it can bind to composite elements that have a (half) GRE and a response element from another transcription factor. GR binding can either make transcription work or stop it. The GR can also physically interact with other transcription factors to modify their activity, allowing it to indirectly bind to DNA as a monomer. In the past, monomeric GRs tethered to pro-inflammatory transcription factors like NF-B and AP-1 were thought to mediate the anti-inflammatory action of glucocorticoids. On the other hand, dimeric GRs transactivating gene expression through GRE binding were thought to be the cause of side effects like hyperglycaemia from glucocorticoid treatment. However, the picture has become increasingly complex in recent years.

Description

The majority of these insights are derived from in vitro and in vivo experiments in which the function of a dimer-deficient mutant GR caused by a point mutation in the dimerization interface of the DNA binding domain is investigated. Although it has been demonstrated to bind DNA and even increase GRE-dependent transactivation of a small number of genes, this GRdim mutation typically shifts the balance of GR-mediated gene regulation to dimerization-independent mechanisms like tethering, raising questions about whether it is completely dimerization-deficient. In a few mouse models for provocative sicknesses, the remedial glucocorticoid impact is flawless in GRdim faint mice, which is in accordance with a significant pretended by monomeric GR. However, other models, particularly those that mimic acute inflammatory conditions like systemic inflammatory response syndrome and sepsis, show that these mutant mice have a significantly reduced response to glucocorticoids. GR dimers are thought to elicit these effects by trans activating genes encoding anti-inflammatory proteins and suppressing the transcription of genes encoding pro-inflammatory genes for example, by binding to specific nGREs and this observation suggests that they represent the primary mechanism mediating the therapeutic glucocorticoid action in these circumstances [1,2].

It was demonstrated that some side effects, like osteoporosis, do not require receptor dimerization, making the picture even more complicated. The results of a study on 198 patients with polymyalgia rheumatic or a type of vasculitis are presented in their research article. The majority of the patients were treated with glucocorticoids. The authors discovered no connection between these patients' bone mineral density and glucocorticoid use. They did,

***Address for Correspondence:** Dean Sittig, Department of Medical Informatics, Northwest Permanente, Portland, OR, USA; E-mail: dean.f.sittig@ap.org*

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however, discover a connection between low bone density and treatment with proton pump inhibitors, which are frequently used to lower the risk of gastric ulcer formation caused by glucocorticoids. As per the creators, this last option finding ought to be offered more consideration [3,4].

Researchers are still developing so-called Selective GR Agonists and Modulators (SEGRAMs) on the assumption that partial dissociation will be sufficient to sufficiently shift the therapeutic index, despite the fact that it is now clear that newly developed glucocorticoids that induce a GR conformation that is unable to dimerism will not completely dissociate the anti-inflammatory action from the side effects. Mapracorat and vamorolone, two examples of several steroidal and non-steroidal SEGRAMS, are currently being evaluated in clinical trials. A summary of SEGRAM development in their review article, they also talk about a second way to reduce the side effects of glucocorticoids using Nano formulations to better target drugs to specific tissues or types of cells. In their respective models, the therapeutic ratio of the encapsulated drug was increased by both types of liposomes [5].

Conclusion

Glucocorticoids can be carried by a variety of nanoparticle formulations, including modified exosomes, poly-decalactone methyl-polyethylene glycol-based nanoparticles, and novel inorganic–organic hybrid nanoparticles. There is reason to believe that many of these formulations will soon be put through their paces in clinical trials due to the wide range of these approaches and the favourable outcomes of numerous preclinical studies involving these nanoparticles. Validated biomarkers are required in order to be able to anticipate when patients will become resistant to glucocorticoid therapy and switch to a more effective treatment at the appropriate time. The relationship between glucocorticoid responsiveness and the induction of local cortisol production in the intestines of ulcerative colitis patients was the subject of an extensive study that included experiments conducted on human patient samples, a mouse model, or ganoids, and cell cultures. In the intestinal cells of steroid-dependent and steroid-refractory patients, they discovered elevated cytoplasmic levels of the transcription factor that is known to be involved in intestinal steroid genesis. This suggests that the patients' decreased local cortisol production may be related to this finding.

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Conflict of interest

No potential conflict of interest was reported by the authors.

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