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Review

The novel strategy of glucocorticoid drug development via targeting nongenomic mechanisms

Chun-Lei Jiang [a,*], Lei Liu [a], Zhen Li [b], Frank Buttgereit [c,*]

[a] Laboratory of Stress Medicine, Faculty of Psychology and Mental Health, Second Military Medical University, 800 Xiangyin Road, 200433 Shanghai, PR China
[b] Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 528 Zhangheng Road, 201203 Shanghai, PR China
[c] Department of Rheumatology and Clinical Immunology, Charité University Hospital, 10117 Berlin, Germany

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ABSTRACT

Glucocorticoids (GCs) are widely used in clinical practice as potent anti-inflammatory and immunosuppressive agents. Unfortunately, they can also produce numerous and potentially serious side effects that limit their usage. This problem represents the driving force for the intensive search for novel GCs with a better benefit–risk ratio compared to conventional GCs. GCs are believed to take effects mainly through classical genomic mechanisms, which are also largely responsible for GCs' side effects. However, in addition to these genomic effects, GCs also demonstrate rapid genomic-independent activities. It has become increasingly evident that some of the anti-inflammatory, immunosuppressive, anti-allergic and anti-shock effects of GCs could be mediated through nongenomic mechanisms. Thus, theoretically, trying to use nongenomic mechanisms of GCs more intensively may represent a novel strategy for development of GCs with low side effect profile. The new GCs' drugs will take clinical effects mainly via nongenomic mechanisms and do not execute the classical genomic mechanism to reduce side effects.

Contents

1. Introduction

GCs are steroid hormones that have pleiotropic effects on development, metabolism, cognitive function and other aspects of physiology. As potent anti-inflammatory, immunosuppressive and anti-allergic agents, synthetic GCs have been extremely widely used in clinical practice including the treatment of many inflammatory and atopic diseases.

However, their clinical use is limited by numerous, unpredictable and potentially serious side effects especially with high dosage and prolonged usage. The unwanted side effects include suppression of the hypothalamic–pituitary axis, osteoporosis, reduced bone growth, susceptibility to infections, adverse effects on skin and eyes, acute adrenal failure, behavioral alterations and disorders of lipid metabolism.

* Corresponding author.
E-mail addresses: cljiang@vip.163.com (C.-L. Jiang), frank.buttgereit@charite.de (F. Buttgereit).

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This discrepancy is the driving force for the intensive search for novel GCs with a better benefit–risk ratio compared to conventional GCs. The discovery of nongenomic mechanisms of GCs represented an interesting development, and further insights into the mechanisms may open novel approaches for the therapy of various diseases. Theoretically, a new approach of optimizing GCs therapy could be to develop drugs selectively affecting nongenomic mechanisms, which may be able to produce lesser side effects.

2. The classical genomic mechanism of GCs actions and the development of new drugs

GCs regulate gene expression both positively and negatively. Both of these effects are mediated by the GCs receptor (GR), a ligand-dependent transcription factor, named as genomic mechanisms. Genomic mechanisms of GCs are mediated primarily by the GRs through activation or repression of specific target genes, which normally need several hours to take effect. Upon binding GCs, the cytoplasmic GR undergoes a conformational change, becomes hyperphosphorylated (P), dissociates from accessory proteins, and translocates into the nucleus, where it can exert its genomic effects in 5 primary ways, including: (1) transcriptional activation via binding as a dimer directly to positive glucocorticoid response elements (GREs) found in either the promoters or the intragenic regions of glucocorticoid target genes, (2) transcriptional repression via binding as a monomer directly to negative glucocorticoid response elements (nGREs) in target genes; (3) transcriptional repression or activation via tethering itself, as a monomer or a dimer, to other transcription factors such as NF-κB, c-Jun, and c-Fos; (4), transcriptional repression or activation in a composite manner by binding as a dimer directly to GREs and interacting with other transcription factors; and (5) post-transcriptional modification of transcription factors via transcriptional activating the expression of anti-inflammatory molecules such as glucocorticoid induced leucine zipper (GILZ), MAPK phosphatase 1 (MKP-1) and tristetraproline (TTP) [1–4].

The GCs' critical therapeutic effects are often accompanied by severe and sometimes irreversible side effects. The goal of the development of new GCs is to maintain the anti-inflammatory and immunosuppressive properties of classical GCs, but to reduce side-effect profile. GCs affect gene expression by both transactivation and transrepression mechanisms. Based on the early studies, it was considered that anti-inflammatory effects of GCs are mostly due to inhibition of transcription, whereas the activation of transcription by the GR accounts for the majority of side effects, such as steroid diabetes, require GR–DNA interaction and transactivation, although the molecular mechanisms of GCs-induced side effects are complex and often not yet well understood [5,6].

GR ligands that promote the negative regulatory action of the receptor with reduced positive regulatory function should therefore show an improved therapeutic index. Thus, ligands that preferentially induce the transrepression and not transactivation function of the GR should be as effective as standard GCs but with fewer undesirable effects. So, one goal of the early-age development of new drugs is to identify ligands of the GR, which preferentially induce transrepression with little or no transactivation activity [6,7].

Dissociating transactivation from transrepression completely is so far not possible because of the interdependent nature of the two regulatory processes. Nevertheless, understanding of the molecular mechanisms of the GR has triggered several drug discovery programs and these have led to the identification of dissociated GR-ligands, such as selective GR agonists (SEGRAs) [8–13].

However, till now the dissociation between transactivation and transrepression functions of GR has not been really resolved. Fortunately, the previous dogma that the undesirable side effects of GCs therapy are induced by dimer-mediated transactivation, whereas its beneficial anti-inflammatory effects are mainly due to the monomer-mediated transrepressive actions of GR has been undermined clearly by the new findings, which clearly showing that GR dimer-dependent transactivation is essential in the anti-inflammatory activities of GR. Many of these studies used $GR^{dim/dim}$ mutant mice, which show reduced GR dimerization and hence cannot control inflammation in several disease models [14]. Studies using $GR^{dim/dim}$ mice have shown that in most inflammatory conditions transactivation of anti-inflammatory genes is required for immune suppression. $GR^{dim/dim}$ mice with contact dermatitis did not respond to glucocorticoid therapy. Similarly, in a model of septic shock, $GR^{dim/dim}$ mice showed increased mortality and increased cytokine release compared with wild-type mice, indicating that dimerization and binding of the glucocorticoid receptor to DNA was required for GCs to exert their anti-inflammatory effects. The glucocorticoid-induced, anti-inflammatory proteins such as GILZ and annexin A1 are regulated by GR homodimerization. Moreover, glucocorticoid receptor monomer interference with AP1 was sufficient to cause bone loss [15]. These animal models have shown that the anti-inflammatory and adverse effects of glucocorticoids are mediated by both monomeric and dimeric glucocorticoid receptor binding.

Nevertheless, the development of SEGRAs will continue to be investigated. But the investigators have to improve the screening strategies for identification of SEGRAs. And it is urgently needed to understand further the molecular mechanisms of action of GCs to search for novel GCs that have reduced side effects.

3. The nongenomic mechanism of GCs actions related to clinical usages

It is believed traditionally that GCs exert most of their effects genomically. In addition to the well-known classical genomic mechanisms of GCs action, mounting evidence suggests that GCs also affect various functions via rapid, nongenomic mechanisms [16–19].

The nongenomic GCs mechanisms have been exploited in clinical therapy, where it has become increasingly evident that nongenomic GCs activity may be relatively more important in mediating the therapeutic effects of intermediate-to-high doses of GCs, especially in high-dose pulsed GCs administration [20,21].

Since GCs are widely used clinically as mentioned above, whether nongenomic mechanisms play a part in these clinical applications is attractive for new drug development. It seems that rapid nongenomic GCs effects play an important role, because clinical effects can be rapidly seen following GCs administration especially with high dose application.

3.1. The nongenomic mechanism of GCs in anti-inflammatory and immunosuppressive actions

GCs exert rapid effects on immune cells [22–24,4]. GCs can directly regulate cell adhesion and locomotion by a nongenomic mechanism that is independent of modulation of gene expression [25] and regulate thymocyte apoptosis through a nongenomic GCs signaling pathway [26].

GCs rapidly inhibit the signal transmission pathway mediated by T-cell receptors (TCR) using a nongenomic mechanism that requires the binding of GCs to membrane receptors and not nuclear receptors [27]. GCs also modulate T cells' cytoskeletal architecture by nongenomic mechanisms [28].

Dexamethasone, a synthetic member of the GCs class of hormones that is commonly used to treat chronic inflammatory