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Potential of glucocorticoids to treat intestinal inflammation during sepsis

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Glucocorticoids (GCs) are steroid hormones characterized by their anti-inflammatory and immunosuppressive nature. Although GCs are very commonly prescribed, in several diseases, including sepsis, their clinical treatment is hampered by side effects and by the occurrence of glucocorticoid resistance (GCR). Sepsis is defined as a life-threatening organ dysfunction, initiated by a dysregulated systemic host response to infections. With at least 19 million cases per year and a lethality rate of about 25%, sepsis is one of the most urgent unmet medical needs. The gut is critically affected during sepsis and is considered as a driving force in this disease. Despite there is no effective treatment for sepsis, pre-clinical studies show promising results by preserving or restoring gut integrity. Since GC treatment reveals therapeutic effects in Crohn's disease (CD) and in pre-clinical sepsis models, we hypothesize that targeting GCs to the gut or stimulating local GC production in the gut forms an interesting strategy for sepsis treatment. According to recent findings that show that dimerization of the glucocorticoid receptor (GR) is essential in inducing anti-inflammatory effects in pre-clinical sepsis models, we predict that new generation GCs that selectively dimerize the GR, can therefore positively affect the outcome of sepsis treatment.

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Introduction

Glucocorticoids (GCs) are steroid hormones, produced by the adrenal gland of all vertebrate animals, and widely used in the treatment of various autoimmune, inflammatory and allergic disorders, such as rheumatoid arthritis (RA), lupus erythematosus, inflammatory bowel disease (IBD), transplant rejection and asthma [1]. They work via binding to the glucocorticoid receptor (GR), a member of the nuclear receptor family. Upon ligand binding, GR dislocates from its chaperone complex and translocates to the nucleus. In the nucleus, GR interacts with the genomic DNA or with other proteins to regulate gene transcription of thousands of genes (protein coding, micro-RNA and long non-coding genes). GR can influence gene expression via several ways, but the best known is the GR dimer mechanism, in which GR homodimers bind to glucocorticoid-responsive-elements (GREs) to activate gene transcription. GR can also transcriptionally repress genes by binding, as a monomer to other transcription factors (TFs) such as NF-kB and AP-1, thereby preventing them from activating gene transcription.

GCs are considered to be the most effective anti-inflammatory drugs. It is estimated that about 3% of the Western population are using GCs [2]. However, the therapeutic use of GCs is hampered by the occurrence of side effects such as osteoporosis, hyperglycemia, disturbed fat redisposition, muscle atrophy and hypertension, especially during chronic usage [3]. Furthermore, some patients do not respond to the therapy, a phenomenon called glucocorticoid resistance (GCR). This GCR occurs in diseases such as severe asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease (IBD) and sepsis. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [4]. The incidence of sepsis is still increasing year after year, and hence it remains one of the leading causes of death globally [5]. Unfortunately, sepsis patients only get supportive care, consisting of rapid delivery of antibiotics, fluid resuscitation, vasopressor administration, lung ventilation and nutritional support [6]. Sepsis consists of an early pro-inflammatory phase, causing early deaths. Thanks to improved clinical management, many patients survive this first phase. However, these patients can enter an immunosuppressive status in which they can die because of the inability to clear primary infections as well because of the development of secondary infections [7].

Although sepsis consists of an early pro-inflammatory phase, the systemic delivery of anti-inflammatory GCs has not really led to a breakthrough in sepsis [8,9].

However, experiments with animal models do show the importance of GCs and GR signaling during sepsis. Both injection of GR antagonist RU486 and adrenalectomy sensitize mice for tumor necrosis factor alpha (TNFα)-induced systemic inflammatory response syndrome (SIRS) [10,11]. Furthermore, mice carrying mutant GR alleles, for example, the GR^{dim} mice which have a point-mutated GR with reduced transcriptional activity, are very sensitive in SIRS and sepsis models [12–15]. Also GR signaling in T-cells, dendritic cells and macrophages has shown to be important, since mice with conditional ablation of GR in these immune cells exhibit higher mortality in different sepsis models [12,16–19]. In addition, intestinal GR has shown to be important in the protection against TNFα-induced systemic inflammation [13].

These results show that there still could be a future in the use of GCs in sepsis, provided that a number of essential questions about GR in sepsis are addressed. One major question is if GCs can be made really efficient in sepsis, if we target them to the right cells. Multiple components of the host response are involved in the mortality of sepsis, but the gut is seen as the motor of sepsis and multiple organ dysfunction [20]. Since GC treatment reveals therapeutic effects in Crohn's disease (CD) and in pre-clinical sepsis models, we hypothesize that targeting GCs to the gut or stimulating local GC production in the gut forms an interesting strategy for sepsis treatment.

Intestinal damage in sepsis

The gastrointestinal tract is composed of the mouth, the esophagus, the stomach, the small intestine (subdivided into duodenum, jejunum and ileum) and the large intestine (subdivided into cecum, colon, rectum and anal canal). The inner layer of the intestine consists of IECs and separates the underlying tissue from the external environment. The IECs absorb nutrients from the food and interact with the microbiome and yet exclude pathogens, toxins and allergens. When this process is impeded, intestinal homeostasis is disturbed and disease may occur.

The small intestine is organized in villi, interspersed by the crypts of Lieberkühn. The crypts contain $Lgr5^{+}$ stem cells that renew the IECs of the villi and Paneth cells, that secrete anti-microbial peptides and proteins (AMPs), for example, lysozyme and α-defensins, and create the ideal environment for the stem cells [21,22]. The small intestinal villi contain different IECs such as absorptive enterocytes, mucus-producing Goblet cells, hormone-producing enteroendocrine cells, Tuft cells important in parasitic infections and M-cells that are important for the uptake of luminal antigens and presentation to the immune system [23]. Each of these differentiated IECs has unique specific functions to protect the host from external insults and to maintain intestinal homeostasis. The IECs are covered by a mucus layer, forming the first barrier between the IECs and the lumen. Goblet cells secrete mucins and additional proteins such as trefoil factor peptides to maintain mucosal homeostasis [24]. Adjacent IECs are interconnected by tight junctions (TJs) that form paracellular seals for preventing the flux of hydrophilic molecules [25]. TJs are multiprotein complexes composed of integral membrane proteins (claudins, occludin and junctional adhesion molecules, JAMs) and peripheral membrane associated proteins (zonula occludens, ZO) linked to the actine-myosin cytoskeleton. Cell–cell communication and exchange of substances is further regulated by adherens junctions and gap junctions. The IECs also communicate and interact with the underlying gut-associated lymph tissue (GALT) for regulating the immune response.

During sepsis, pathogen-associated molecular pattern molecules (PAMPs) expressed on invading organisms are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) present on different cells in the body, such as immune cells. PRR activation on macrophages induces intracellular signaling cascades, characterized by the release of pro-inflammatory molecules, such as TNFα, interleukin (IL)-1β and IL-1α. This cytokine storm leads to systemic inflammation.

It is believed that this inflammatory response affects the gut integrity on different levels. In the epithelium, an increase in cell death, and a decrease in proliferation and migration of IECs is observed [26]. Alterations in TJs will further lead to intestinal permeability [27,28]. These alterations include redistribution of the TJ proteins occludin and claudins (1, 3, 4, 5 and 8) [28]. Furthermore, there is an increase in expression of myosin-light chain kinase (MLCK), which phosphorylates myosin light chain leading to cytoskeletal contraction and junction disruption [29]. Also, the mucus layer is damaged, which further leads to epithelial cell dysfunction. The increased intestinal permeability can lead to bacterial translocation via the portal circulation [30]. Toxic mediators can also be transported through the mesenteric lymph nodes (MLN) to cause distant organ damage [31]. Finally, the microbiome is converted into a 'pathobiome' characterized by an increase in pathogenic bacteria and an induction of virulence factors in commensals [32]. This pathobiome can manipulate and dysregulate the immune system. The local gut injury can further lead to distant injury and multiple organ dysfunction in sepsis.

Glucocorticoids in the treatment of sepsis to ameliorate gut damage

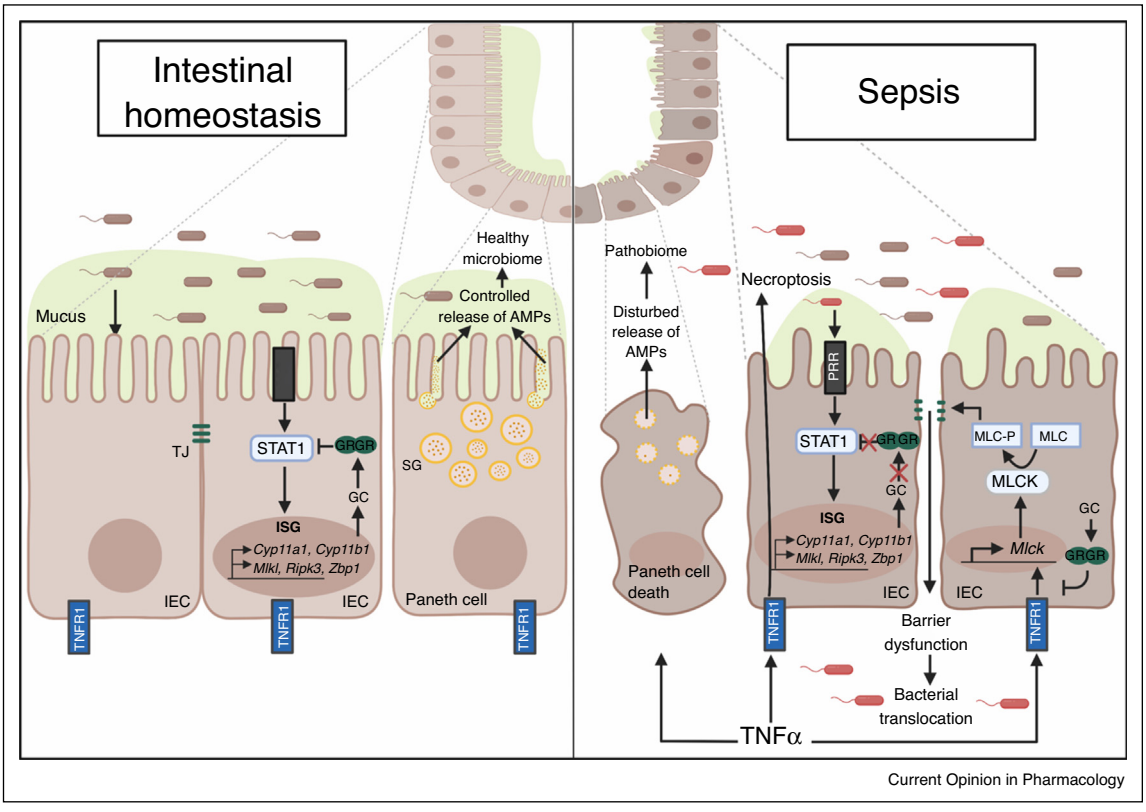
Currently, no therapy exists that targets the gut epithelium, hyperpermeability or mucus in sepsis patients. However, pre-clinical sepsis studies show interesting interventions aimed at restoring the intestinal barrier. These studies are associated with improvements in survival in animal models of critical illness [33,34]. Administration of systemic epidermal growth factor (EGF) after the onset of the

infection decreased mortality in pneumonia-induced and polymicrobial-induced sepsis mouse models. Interestingly, the survival advantage was associated with improved intestinal integrity and decreased apoptosis and increased villus lengths [34,35]. Besides, gut-specific inhibition of apoptosis leads to higher survival rates in preclinical sepsis [34]. The above mentioned studies reveal promising results by targeting the gut in sepsis.

In addition, we believe that GCs can be used to ameliorate intestinal damage in sepsis (see Figure 1). It is well established that GC therapy leads to normalization of intestinal permeability in Crohn's disease (CD) patients [36]. GR inhibits MLCK protein expression by inhibiting TNFα-induced upregulation of MLCK promoter activity [35]. TNFα is one of the most powerful and abundant cytokines in sepsis [37]. Also, knockout of MLCK has been shown to improve gut barrier and survival in an animal model of polymicrobial sepsis, the cecal-ligation and puncture (CLP) model [38]. GCs have been shown to protect against TNFα-induced lethal shock and TNFα-induced intestinal permeability [13,39], and GCs alleviate TNFα-induced goblet- and Paneth cell dysfunction [39].

Besides the effects of GCs on MLCK, it was recently shown that GCs control STAT1-regulated interferon (IFN) signature in the IECs, in a GR dimer-dependent way [13]: GR^{dim} mice, which express a GR protein with much weaker dimerization and DNA-binding functions, were used. GR^{dim} mice show a constitutive, IEC-specific high expression of hundreds of 'interferon-stimulated genes' (ISG), which make them more vulnerable for TNFα-induced shock and intestinal permeability. A synthetic GC, dexamethasone, was unable to protect

Figure 1



Proposed mechanism of intestinal damage during sepsis compared to intestinal homeostasis and mechanisms where glucocorticoids (GCs) can protect. The inflammatory cytokine storm (e.g. TNFα) during sepsis affects the gut on several levels. TNFα signaling upregulates MLCK, a protein that phosphorylates MLC (MLC-P). MLC-P drives cytoskeletal contraction followed by tight junction (TJ) disruption. TJ rupture leads to barrier dysfunction and subsequently to bacterial translocation. GCs can inhibit MLCK protein expression by impeding TNFα-induced upregulation of MLCK promoter activity. Besides, the microbiota communicates with intestinal epithelial cells (IECs) by pathogen recognition receptors (PRRs). PRR signaling leads to STAT1 upregulation followed by an interferon stimulated gene (ISG) signature, for example, genes involved in necroptosis (*Ripk3, Zbp1* and *Mlkl*). Genes involved in local GC production (*Cyp11a1* and *Cyp11b1*) are upregulated to control this ISG signature. However, in sepsis GC resistance occurs, leading to failure of the protective mechanism of GCs. Furthermore, TNFα stimulates STAT1 and ISG, leading to excessive necroptosis. TNFα also leads to mucus depletion, Paneth cell death and loss of antimicrobial peptides (AMPs). Decreased release of AMPs further promotes the pathobiome observed in sepsis. *Abbreviations. AMP: antimicrobial peptide, GC: glucocorticoid, GR: GC receptor, IEC: intestinal epithelial cell, ISG: interferon stimulated genes, PRR: pattern recognition receptor, SG: secretory granules, TJ: tight junction.*
Figure created with BioRender.com.

these mice against TNFα-induced lethality and permeability, showing the importance of GR dimerization. Tofacitinib, a non-selective oral small molecule JAK inhibitor, however could protect these mice against a lethal dose of TNFα [13]. The data reveal that GCs/GR, via a dimer pathway, constitutively repress ISRE/IRF pathways in IECs, presumably via STAT-1 repression, and that a failure to repress this key pathway leads to sensitivity to TNFα-induced cell death and lethal shock.

Recently, it was shown that IFN-λ induces Paneth cell death via activation of STAT1 and MLKL in mice [40]. Biopsies of CD patients show higher levels of IFN-λ, systemically and in the ileum. This was associated with cell death in the crypt and a decrease in Paneth cells. IFN-λ levels were also shown to be elevated in clinical and experimental sepsis [41]. Neutralization of IFN-λ protected mice from CLP-induced sepsis, while IFN-λ administration increased mortality [41]. It is suggested that IFN-λ might impair bacterial clearance by restriction of neutrophil influx to the site of infection, leading to a failure in clearing the infection. Besides, IFN-λ controls Paneth cell extrusion and secretion of antimicrobial mediators, which may affect the microbiome and the epithelial integrity in the gut [42••]. The effects of IFN-λ neutralization on the intestinal damage seen in sepsis needs further investigation.

Looking for a 'next generation' glucocorticoid therapy?

Systemic delivery of GCs has not really led to a breakthrough in sepsis [43–45]. There may be many reasons behind this observation. But because of the previous paragraphs, according to us, it would make sense (1) to generate GCs that stimulate maximal GR dimerization and (2) to address these GCs specifically to the IECs. An old dogma states that the side effects of GC therapy are due to GR dimer activated genes playing a role in glucose synthesis and fat metabolism. The anti-inflammatory effects were believed to be monomer-mediated by repressing inflammatory TFs such as AP-1 and NF-kB. This dogma has led to a search for 'selective GR agonists and modulators' (SEGRAMs), yielding only a few molecules in clinical use. However, in some diseases, GR dimerization has shown to be indispensable for its anti-inflammatory effects. As mentioned, GR^{dim} mice, have been shown to be very sensitive for several acute triggers, for example, TNFα-induced lethality and intestinal damage [13,14]. Furthermore, they display higher susceptibility for other acute inflammation models such as LPS-induced endotoxemia and the CLP sepsis model [12]. Therefore the SEGRAMs concept needs to be redefined into selective monomerizing GR agonists and modulators (SEMOGRAMs) and selective dimerizing GR agonists and modulators (SEDIGRAMs) for therapeutic applications in chronic and acute inflammatory disorders respectively [46]. Recently two compounds were identified as SEDIGRAMs, namely Cortivazol and AZD2906. Both compounds conferred strong protection in a mouse model of TNFα-induced lethality [47]. Whether such components indeed hold promise in sepsis still needs to be shown.

The second strategy is to modulate pharmacokinetics and cell-specific targeting of GCs. For the application in IBD, so-called 'second-generation steroids' were developed, for example, budesonide and beclomethasone dipropionate (BDP) [48]. These new formulations of GCs minimize systemic bioavailability to decrease side effects. Budesonide makes use of an extensive first-pass liver metabolism, leading to reduced systemic side effects. BDP has high topical effects and low systemic activity. It is administered as a prodrug that is activated by hydrolysis upon release. Enteric-coated oral formulations of budesonide and BDP make use of a gastro-resistant and pH-dependent coating around the GCs, to withstand attack by stomach acid and to ensure release in the small intestine and colon. The many available conditional GR knockout mice show that GC modulate distinct cell types in each individual disease [49]. New delivery vehicles have been developed including PEGylated liposomes, polymeric micelles, polymer-drug conjugates, inorganic scaffolds, and hybrid nanoparticles [50,51]. Several studies examined the therapeutic potential of oral administration of nanoparticles in IBD animal models [52–56]. Targeting of GCs to the intestine in sepsis however needs to be investigated.

A third strategic option would be to stimulate GC production in the intestine itself. GCs are not only produced by the adrenals, but also locally by the intestinal epithelium. These local GCs contribute to the immune homeostasis of the intestinal mucosa and defective intestinal GCs production has been associated with development of IBD [57]. Liver-Receptor-Homolog-1 (LRH-1) is a nuclear receptor involved in various biological processes, like steroidogenesis. A strong correlation was observed between LRH-1 and steroidogenic enzymes in intestinal biopsies of pediatric IBD patients [57]. It is believed that LRH-1 regulates intestinal immunity by stimulating local GC production. This observation makes LRH-1 an attractive molecule to target in IBD or other inflammatory diseases, like sepsis.

Conclusions

Despite increasing knowledge about the molecular mechanisms in the pathogenesis of sepsis, current treatments are mainly limited to antibiotic treatment and support of vital functions. Even GCs, the most potent anti-inflammatory drugs, have not led to major therapeutic advances. The gut has been hypothesized as the 'motor' in sepsis, as the gut integrity and intestinal homeostasis are critically affected in sepsis and this leads to both local as distant damage, resulting in multiple organ failure. GCs have been shown to have ameliorating effects on the intestine, both in IBD

patients, as in sepsis pre-clinical models. Therefore, we believe we can use GCs for the treatment of sepsis-induced gut damage, thereby preventing subsequent organ damage and lethality. For this, some optimization of the current GCs can improve the therapeutic effects.

First of all, we believe in the use of SEDIGRAMs for sepsis, as dimerization of GR is clearly important in the protection in different SIRS/sepsis mouse models and intestinal damage. Besides controlling ISG in the IECs, SEDIGRAMs also have the advantage of inducing GR dimer-dependent anti-inflammatory molecules, like glucocorticoid-induced leucine zipper (GILZ). In sepsis patients, the expression of the coding gene of GILZ is hampered in white blood cells and pre-clinical sepsis studies already proved that overexpression of GILZ could improve survival rates [58].

Another option is to look downstream. GR dimers are important in the suppression of ISGs, containing necroptosis related genes. GR^{dim} mice show an increased expression of ISGs in their intestine, leading to an increased sensitivity for TNFα-induced lethality and intestinal damage. The JAK/STAT inhibitor tofacitinib could protect these mice. Tofacitinib has recently been investigated in CD and UC patients. In CD, tofacitinib showed an anti-inflammatory effect but failed to demonstrate a significant response and remission rate [59]. In UC, better results were obtained in phase III trials and tofacitinib has recently been authorized for marketing by the FDA and EMA for UC patients [60,61•]. Inhibiting the JAK/STAT pathway impairs the immune response against viral and bacterial infections: for example, IFNAR−/− mice are supersensitive for viral infection [62]. This challenges the utility of JAK/STAT inhibition in patients. Indeed, overall infections, specifically serious infections, were higher in treated versus placebo groups [60]. In addition, treated patients showed more cases of non-melanoma skin cancers, cardiovascular events and increased serum lipid levels. Selective JAK1 blockers are now being investigated.

A final option is to target GCs towards the intestine. Second-generation corticosteroids are compelling candidates as they reduce side effects, lower systemic toxicity and have high topical activity at the gut level [63]. Their general mechanism of action is based on novel drug-targeting methods that lower systemic bio-availability of the GCs. Promising results for these drugs are observed in IBD and research suggests a beneficial role in sepsis treatment as they can be seen as gut-targeting GC. The use of drug-loaded nanoparticles further lead to enhanced therapeutic efficacy compared to conventional IBD drugs in pre-clinical IBD studies [55]. The ability of oral GC-loaded nanoparticles to accumulate in inflamed regions of the gut [64,65], makes nanoparticles an attractive drug delivery method to further investigate in sepsis patients.

Conflicts of interest statement

Nothing declared.

CRediT authorship contribution statement

Kelly Van Looveren: Writing - original draft, Writing - review & editing. **Charlotte Wallaeys:** Writing - original draft, Writing - review & editing. **Claude Libert:** Writing - original draft, Writing - review & editing.

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