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Review

Critical Roles of Endogenous Glucocorticoids for Disease Tolerance in Malaria

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During malaria, the hypothalamic–pituitary–adrenal (HPA) axis is activated and glucocorticoid (GC) levels are increased, but their essential roles have been largely overlooked. GCs are decisive for systemic regulation of vital processes such as immune responses, vascular function, and metabolism, which are crucial in malaria. Here, we introduce GCs in general, followed by their versatile roles for disease tolerance in malaria. A complementary comparison is provided with their role in sepsis. Finally, potential translational implications are considered. The failed clinical trials of dexamethasone against cerebral malaria in the past have diminished the interest in GCs in malaria. However, the issue of relative corticosteroid insufficiency has barely been explored in malaria patients, but may hold promise for a better understanding and treatment of specific malaria complications.

Highlights

Like other severe systemic infections, malaria leads to stimulation of the HPA axis, resulting in increased GC levels.

The essential roles of GCs for disease tolerance in malaria have been largely overlooked. GCs are decisive to survive malaria via the regulation and integration of vital systemic processes such as immune reactions, metabolism, and vascular function.

Existing evidence of the function and possible dysregulation of the HPA axis in malaria is scarce, but may hold the key to a better understanding and treatment of specific malaria complications.

The failure of clinical trials with GCs against cerebral malaria preluded the neglect of GCs in the malaria field, but the therapeutic impact on other complications or patient subsets is unknown.

Disease Tolerance in Malaria

Malaria is a parasitic disease that poses a major health burden to the world with an estimated 219 million cases and 435 000 deaths in 2017 [1]. The outcome of infection with *Plasmodium* ranges from asymptomatic infection in semi-immune individuals to uncomplicated malaria (UM) and complicated/severe malaria (SM). Complications of malaria contribute to the majority of deaths and include cerebral malaria (CM), severe malarial anemia, placental malaria and **malaria-associated acute respiratory distress syndrome** (**MA-ARDS**) (see Glossary). The pathogenesis of malaria complications is complex, with several processes taking part, such as parasite sequestration, endothelial activation, and inflammation [2]. Metabolic disturbances, including hypoglycemia and lactic acidosis, are common in malaria and contribute significantly to the severity of disease, but they remain poorly understood [3,4]. The pathophysiology of hypoglycemia in malaria is often explained by increased glucose consumption by hypoxic tissues, the febrile host and the parasite, inadequate food intake, and insufficient glucose production, possibly due to decreased liver perfusion [5].

Disease tolerance relies on host defense mechanisms that limit the pathological consequences of the infection without interfering with the parasite load [6–8]. It remains unclear why some patients progress from UM to SM and lose their disease tolerance. Defining the mechanisms of tolerance in malaria is extremely important, since these may help to design new treatments to combat the detrimental progression of disease. Several studies indicate the importance of glucose metabolism in disease tolerance to malaria. Cumnock *et al*. suggested that, in a nonlethal murine model of malaria, the combination of anorexia and severe anemia makes the host more reliant on glycolysis, which is essential for survival [9]. Contrarily, in the lethal experimental cerebral malaria model, Wang *et al*. showed that blocking glycolysis prolonged survival [10]. In general, the host nutritional status is important for the outcome of infection. For instance, dietary restriction affects the host response to the parasite in the spleen and liver [11,12]. Metabolic adaptations of the host were also associated with disease tolerance in bacterial and viral infections [13,14]. Tolerance mechanisms in malaria include also anti-inflammatory and pro-resolving processes that do not influence pathogen clearance but alleviate immunopathology. For instance, in several models interleukin (IL)-10 protects malaria-infected mice against lethal disease without decreasing peripheral parasitemia [15].

A severe systemic infection is stressful and induces a neuroendocrine response that aims to restore homeostasis and thus to promote tolerance. One of the most essential responses is the activation of the **hypothalamic–pituitary–adrenal (HPA) axis** that results in glucocorticoid (GC) production [16]. Upon malaria infection, circulating GC levels increase (see Table S1 in the supplemental

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information online). Because endogenous GCs exert various effects, their role in malaria is of great interest and is discussed in this review. We start by introducing GCs and their effects, followed by their role in murine malaria and the potential implications for human malaria.

Production and Clearance of Endogenous Glucocorticoids

Endogenous GCs, that is, cortisol in humans and corticosterone in rodents, regulate a wide range of physiological processes. They are synthesized upon stimulation of the HPA axis [17] (Figure 1, Key Figure). In normal conditions, the axis is stimulated in a circadian and pulsatile manner leading to a GC peak in the morning in humans and in the evening in mice, due to opposite diurnal rhythms. The HPA axis is further activated in conditions of stress – for example, psychological distress, physical strain, tissue trauma, and inflammation – by both neural and nonneural routes [18,19]. Terminal nerve endings of afferent autonomic nerves express several receptors that can sense pathogens or cytokines in tissues. Cytokines such as IL-1β, tumor necrosis factor (TNF)-α, and IL-6 are potent inducers of the HPA axis response. The resulting signaling is projected to the hypothalamus via autonomic nuclei in the brainstem. Moreover, circulating inflammatory mediators can access brain sites via circumventricular organs or via inflammation-mediated breakdown of the blood–brain barrier. The paraventricular nucleus of the hypothalamus secretes **corticotropin-releasing hormone** (**CRH**), consecutively leading to the secretion of **adrenocorticotropic hormone** (**ACTH**) or corticotropin by the anterior pituitary gland (Figure 1). ACTH then stimulates the production of GCs by the adrenal cortex. When the stress subsides, GCs finally exert a negative feedback on both CRH and ACTH production.

The classical CRH–ACTH–GC axis is complemented by direct stimulation of the pituitary or adrenocortical cells. ACTH release from pituitary cells can be directly induced by IL-1, IL-2, or vasopressin [20,21]. ACTH-independent induction of GC synthesis is possible by direct ligation of Toll-like receptor 2 (TLR2) and TLR4 in adrenocortical cells [22]. GC synthesis or steroidogenesis from cholesterol mainly originates in the adrenal cortex (Figure 2), although some production has also been reported in the thymus, intestine, skin, and brain [23].

Of the cortisol/corticosterone that is released into the circulation, approximately 5% is free and thus active, 20% is bound to albumin, and the remaining 75% is tightly bound to **corticosteroid-binding globulin** (**CBG**) [24]. CBG is responsible for the systemic distribution of GCs and the delivery to tissues. Neutrophil elastases can cleave CBG, and therefore more bioactive GCs might be liberated at inflammatory sites [25].

The principal routes of cortisol clearance occur in the liver, through **A-ring reductases**, and in the kidney, through **11β-hydroxysteroid dehydrogenase** type 2 (11β-HSD2; Figure 2). The inactivation by 11β-HSD2 prevents high-affinity binding of GCs to the mineralocorticoid receptor (MR), to enforce specific aldosterone binding. Within cells, the inactive cortisone or 11-dehydrocorticosterone is reactivated by 11β-HSD1 into, respectively, cortisol or corticosterone. These enzymes contribute daily to 30–40% of the total cortisol turnover [26]. Whereas the expression of 11β-HSD2 is mostly restricted to the distal nephron of the kidney, sweat and salivary glands, and colonic epithelium, 11β-HSD1 is widely expressed and is regulated by inflammatory signals, including TNF-α and IL-1β [27]. GCs furthermore induce 11β-HSD1 and suppress 11β-HSD2 expression, which in turn amplifies GC availability [27].

Endogenous Glucocorticoids Exert a Wide Range of Effects

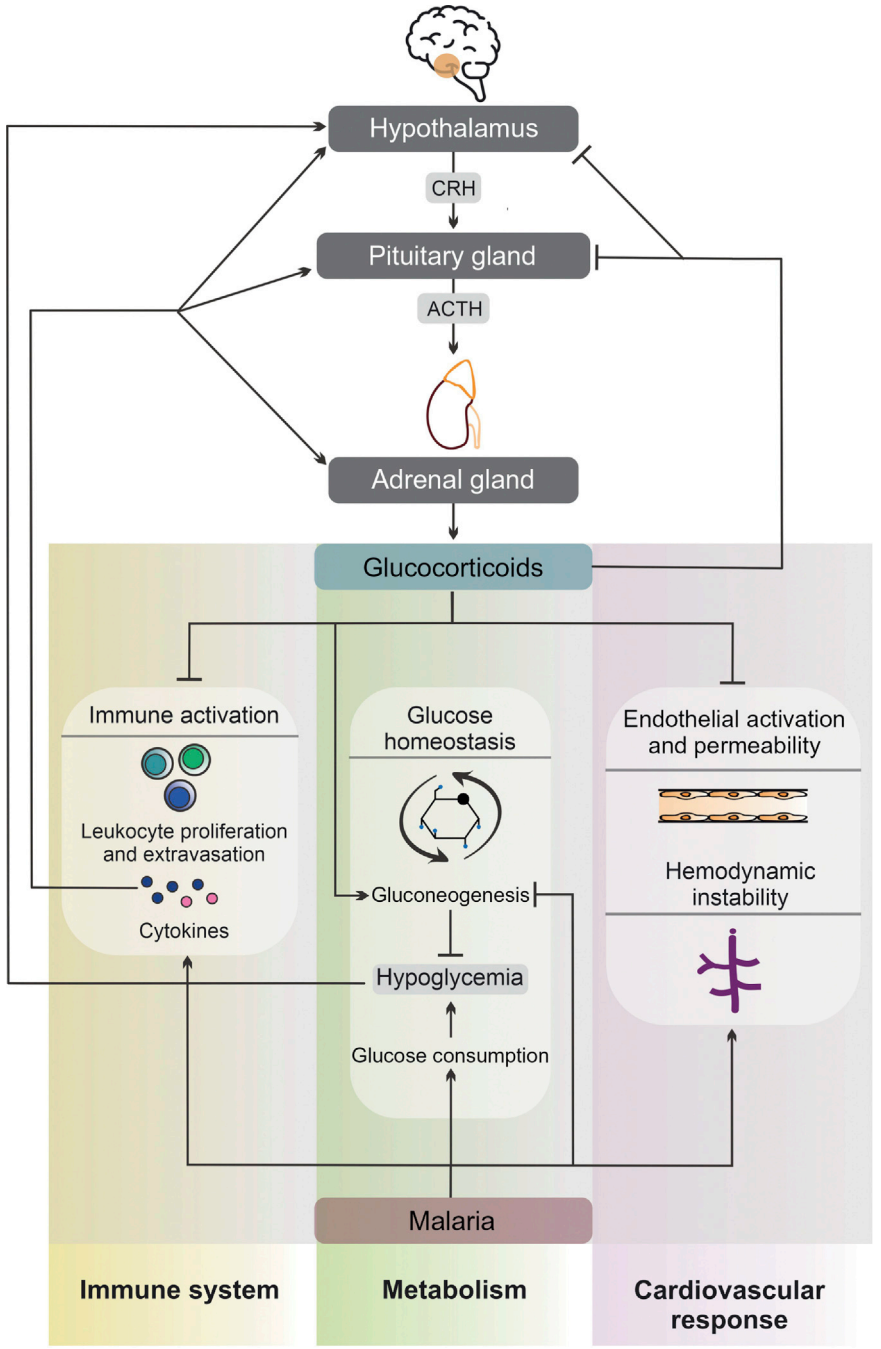
GCs are lipophilic and diffuse easily through cell membranes. Once inside the cytosol, GCs bind to the glucocorticoid receptor (GR), which is expressed by almost all nucleated cells (Figure 3). The GR localizes in the cytoplasm in a multiprotein complex comprised of heat shock proteins, immunophilins, and other chaperones [28]. When GCs bind to the receptor, liganded GR can translocate to the nucleus to interact with DNA and other proteins as a monomer, homodimer, or even a tetramer [25,29,30]. As a genuine transcription factor, GR activates or represses gene transcription of up to 20% of all genes, depending on the target tissue [25]. Besides the genomic effects that affect

Glossary

11β-hydroxysteroid dehydrogenase: the two isozymes 11β-HSD1 and 11β-HSD2 catalyze the interconversion of active cortisol and corticosterone with inactive cortisone and 11-dehydrocorticosterone. 11β-HSD1 is expressed in most cells and acts predominantly as a reductase to catalyze the reactivation of GCs. 11β-HSD2 mainly inactivates GCs to ensure aldosterone agonism of the mineralocorticoid receptor. 11β-HSD2 expression is largely restricted to the distal nephron, sweat and salivary glands, and colonic epithelium.
A-ring reductases: hepatic 5α-reductase and 5β-reductase yield dihydrometabolites of endogenous GCs that are further reduced to generate polar metabolites that can be rapidly cleared by the kidneys (Figure 2).
Adrenal gland: a gland located above the kidney; it produces several hormones. The outer cortex synthesizes GCs, the mineralocorticoid aldosterone, and androgens. The inner medulla synthesizes the catecholamines, adrenalin, and noradrenalin.
Adrenalectomy: the surgical removal of the adrenal glands.
Adrenocorticotropic hormone (ACTH): a hormone secreted by corticotroph cells of the anterior pituitary in response to CRH. ACTH binds to the melanocortin receptor 2 on cells of the adrenal cortex, leading to the synthesis of GCs and, to a lesser extent, aldosterone.
Corticosteroid-binding globulin (CBG): also known as transcortin. CBG is an alpha-globulin produced by the liver, which binds and transports corticosteroids and other steroid hormones.
Corticotropin-releasing hormone (CRH): a hormone released by the paraventricular nucleus of the hypothalamus as part of a daily circadian rhythm or a centrally driven stress response. After secretion, CRH reaches the anterior pituitary where it regulates ACTH secretion.
CRH stimulation test: a test of the HPA axis function with administration of CRH. This leads to ACTH secretion by the pituitary and adrenal cortisol production.

Key Figure

Endogenous Glucocorticoids (GCs) Integrate the Regulation of Immune, Metabolic, and Cardiovascular Homeostasis to Counteract Pathophysiological Processes in Malaria



(Figure legend at the bottom of the next page.)

Dexamethasone suppression test: a test of HPA axis function with administration of dexamethasone, a synthetic GC. This leads to an increased negative feedback on the pituitary, resulting in lower ACTH and lower cortisol plasma levels.
Gluconeogenesis: generation of glucose from precursors, mainly lactate, alanine, or glycerol. Gluconeogenesis especially takes place in the liver and to a lesser extent in the cortex of the kidneys.
Glycogen: a multibranched polysaccharide of glucose that represents the main storage form of glucose, particularly present in the liver and skeletal muscle.
Hypophysectomy: the surgical removal of the pituitary gland or hypophysis.
Hypothalamic–pituitary–adrenal (HPA) axis: an interactive neuroendocrine unit that functions through direct hormone stimulation and feedback interactions, key for basal homeostasis and physiological responses to stress.
Malaria-associated acute respiratory distress syndrome (MA-ARDS): a severe respiratory complication of malaria associated with alveolar inflammation, damage to the alveolar-capillary membrane, alveolar edema, and severe hypoxemia, altogether leading to a poor prognosis.
Metyrapone suppression test: a test of the HPA axis function with administration of metyrapone, which inhibits adrenal cortisol production. This leads to increased ACTH plasma levels due to less negative feedback on the pituitary. Suboptimal ACTH increases in this test are indicative of HPA axis dysfunction.
Vasopressor: an agent that causes a rise in blood pressure by vasoconstriction.

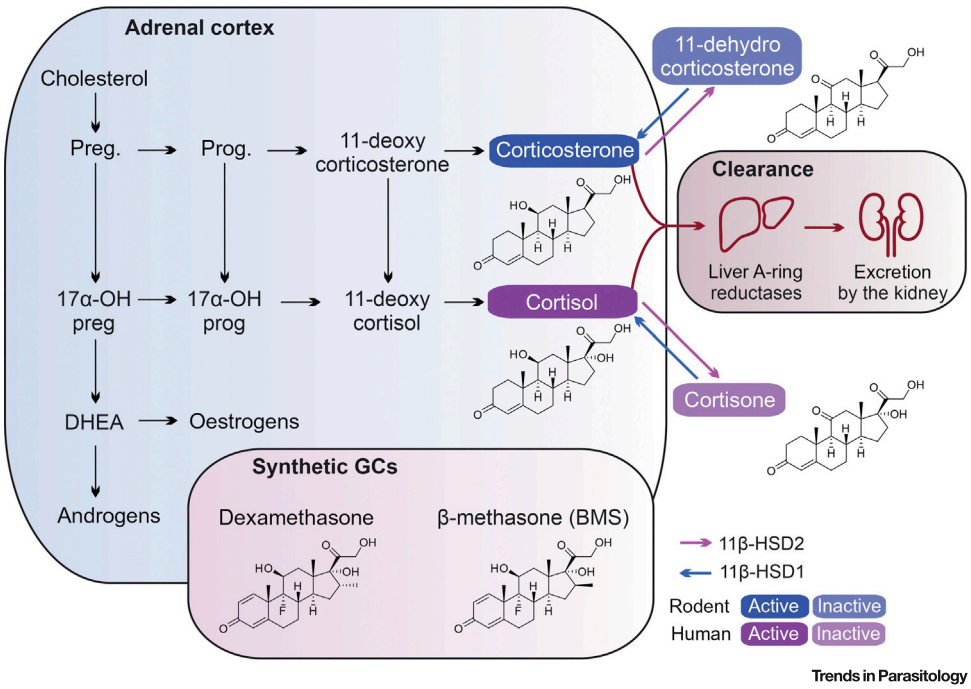


Figure 2. Adrenal Biosynthesis and Clearance of Glucocorticoids (GCs).
This scheme summarizes the synthesis of endogenous GCs from cholesterol in the adrenal cortex. Enzymatic conversions are shown as arrows. Active GCs – corticosterone in rodents and cortisol in humans – are released into the circulation and are either cleared through A-ring reductases in the liver or through 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), mainly in the kidney. The inactive cortisone or 11-dehydrocortisone that is generated by 11β-HSD2, is reactivated within cells by 11β-HSD1 into, respectively, cortisol or corticosterone. Synthetic GCs are used in the treatment of various disorders, including asthma, dermatitis, and rheumatoid arthritis. The drugs that are mentioned in this review are depicted here. Abbreviations: 17α-OH preg, 17α-hydroxy-pregnenolone; 17α-OH prog, 17α-hydroxy-progesterone; BMS, β-methasone hemisuccinate; DHEA, dehydroepiandrosterone; Preg, pregnenolone; Prog, progesterone.

transcription of target genes and take hours, also nongenomic effects of GCs have been described, which manifest rapidly (seconds to minutes) and do not require protein synthesis [25,31]. Mechanisms include intercalation of GCs into membranes, signaling through a membrane-bound GR, interaction with cytoplasmic kinases, and induction of apoptosis by mitochondrial translocation of the

Figure 1. The hypothalamic–pituitary–adrenal (HPA) axis is profoundly stimulated in conditions of stress, for example, inflammation. Both neural and nonneural routes activate the paraventricular nucleus of the hypothalamus that secretes corticotropin-releasing hormone (CRH), consecutively leading to the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. ACTH in turn activates the production of GCs by the adrenal cortex. GCs then exert a negative feedback on both CRH and ACTH production. GCs influence many processes that are essential to survive systemic infections, including malaria. Their immune modulating effects include the inhibition of leukocyte extravasation, proliferation, and activity, and interference with downstream proinflammatory signaling and cytokine function. In malaria, the balance between immune-mediated clearance of the parasite and inflammation dictates host survival and is coregulated by GCs. GCs mediate metabolic effects, especially under stress or fasting conditions, by increasing circulatory glucose by supporting gluconeogenesis, counteracting insulin, and decreasing peripheral glucose uptake. Hypoglycemia is common in malaria and associates with a poor outcome. Malaria infection in mice suppresses gluconeogenesis, and in the absence of GCs severe hypoglycemia occurs. GCs furthermore have vascular effects by preventing vasodilatation, by supporting intravascular fluid retention, and by inhibiting endothelial activation. This might also be important to limit pathogenicity in malaria, since severe malaria is associated with hemodynamic instability (hypovolemia and hypotension), extensive endothelial activation, and loss of barrier function.

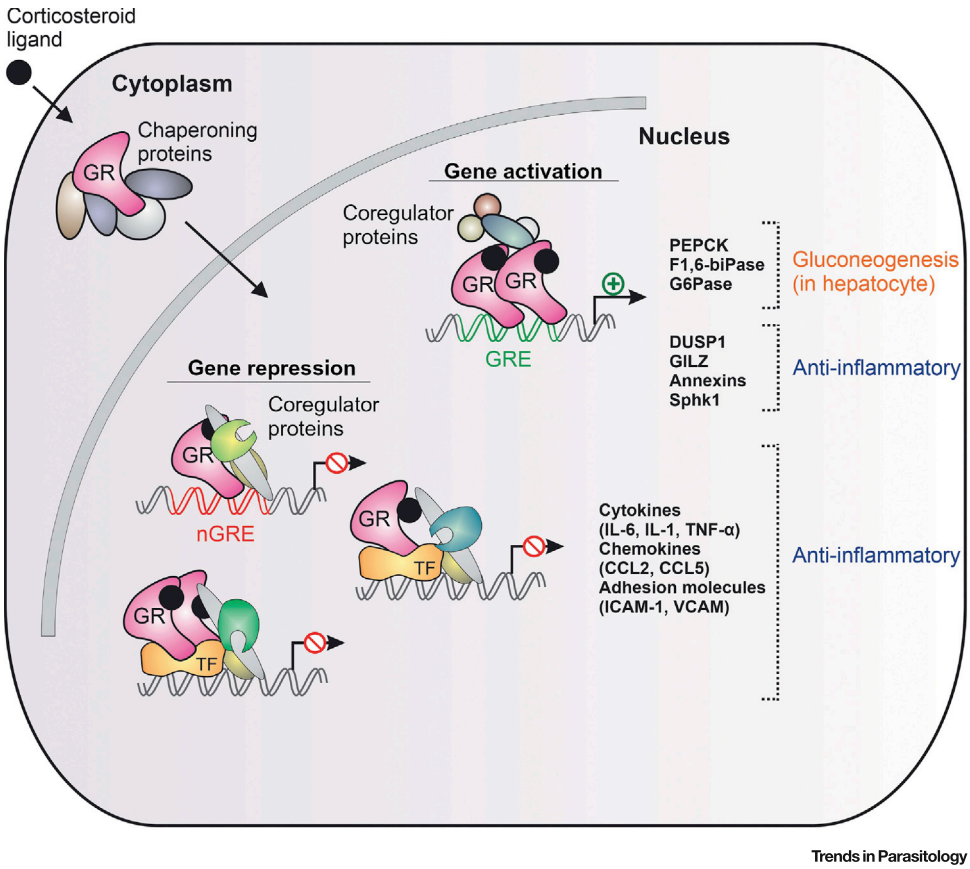


Figure 3. The Glucocorticoid Receptor Influences Gene Expression by Several Molecular Mechanisms.
In its nonliganded state, the glucocorticoid receptor (GR, pink shape) is predominantly cytoplasmic and in complex with chaperoning proteins. Upon binding corticosteroid ligand (filled black circle), GR accumulates in the nucleus, where it influences gene expression as a transcription factor. By virtue of glucocorticoid response elements (GRE, green), GR typically binds onto promoters of target genes as a dimer as one mechanism to activate its target genes. Those include genes that contribute to gluconeogenesis but also anti-inflammatory genes. Target gene repression can be consequent to direct GR binding onto so-called negative GRE elements (nGRE, red) on the DNA or by means of protein–protein interactions, whereby GR can interfere with the activity of other transcription factors (TF, orange shape). In case these transcription factors are proinflammatory [e.g., nuclear factor (NF)-κB, activator protein 1 (AP-1)], the protein–protein interaction mechanism contributes to the anti-inflammatory action of GR. It is still debated to what extent the protein–protein interaction mechanism relies *in vivo* on GR as a monomer or a dimer. Please note that many variants of the simplified mechanisms that are represented here are possible [100]. Abbreviations: DUSP1, dual-specificity protein phosphatase 1; F1,6-biPase, fructose-1,6-biphosphatase; G6Pase, glucose-6-phosphatase; GILZ, glucocorticoid-induced leucine zipper; ICAM-1, intercellular adhesion molecule-1; Il-6, interleukin 6; PEPCK, phosphoenolpyruvate carboxykinase; Sphk1, sphingosine kinase 1; TNF-α, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

ligand-bound GR. Furthermore, in several cell types expressing the MR but not 11β-HSD2, MR may also bind GCs with high affinity and participate substantially in GC signaling [32]. GCs influence many processes ranging from immunity to bone remodeling, cardiovascular function, reproduction, cognition, and metabolism [33].

GCs are well known for their broad immune-modulating effects at multiple levels [25]. In summary, GCs interfere with the downstream proinflammatory signaling of receptors sensing danger signals (pattern-recognition receptors, complement receptors, and Fc receptors). Furthermore, GCs prevent vasodilatation and increased vasopermeability, which are defined hallmarks of inflammation. They

also inhibit cytokine function and leukocyte extravasation. GCs affect various immune cells in a cell-specific way, for example, by inducing apoptosis and changing their differentiation fate or altering their function [34]. GCs are mostly anti-inflammatory, especially during ongoing inflammation or concerning the adaptive immune system. However, proinflammatory effects have been described as well, and they include the upregulation of the expression of NLRP3 and TLRs. This immune-priming role might be important under basal conditions, when GC levels are low, and during the early stages of inflammation, which are controlled by the innate immune response [24,25,31,35,36].

Besides their effects on the immune response, GCs synergize with catecholamines, glucagon, and growth hormone to mediate metabolic effects. The leading metabolic effect of GCs under stress or fasting conditions is the ability to increase circulatory glucose to ensure survival and to provide energy to the brain. GCs mediate the elevation of glucose levels via: (i) increased **gluconeogenesis**; (ii) decreased peripheral glucose uptake; (iii) mobilization of lipids and amino acids through lipolysis and proteolysis; and (iv) counteracting insulin signaling [37]. The pathophysiological consequences of endogenous or exogenous GC excess include hyperglycemia, insulin resistance, fatty liver, obesity, and muscle wasting [37].

Endogenous Glucocorticoid Levels Are Increased in Malaria

The results from studies on GCs in human malaria are summarized and referred to in Table S1. In patients infected with *Plasmodium vivax* and *Plasmodium falciparum*, circulating GC levels are higher compared with healthy controls. Although controversial, GC levels appear higher in patients with CM compared with UM. Cortisol levels decline during treatment as the clinical symptoms and parasitemia decrease. Cortisol levels also increase upon malaria infection of pregnant women. Furthermore, pregnancy-induced cortisol increases might contribute to the higher vulnerability of pregnant women to malaria. This seems particularly the case in primigravidae, in whom cortisol levels, the likelihood of infection, and parasitemia are higher compared with multigravidae. Cortisol levels seem to correlate positively with higher serum IL-10 levels and parasitemia, at least in primigravidae. Interestingly, the increase in GC levels upon malaria infection is conserved, as it was also observed in mice, birds, and lizards [38,39].

Endogenous Glucocorticoids Are Essential for Surviving Malaria and Sepsis

Following decades of intense investigation, gathered insights on the protective effects of endogenous GCs in bacterial sepsis may serve as an example for severe complications in other infectious diseases, including malaria. As indicated in Box 1, SM and sepsis are complex multisystem disorders that share some important clinical characteristics [40]. For instance, a combination of inflammatory and metabolic disturbances is observed in both diseases. GCs are regulators of immunity as well as metabolism, and therefore GC features are likely to show some overlap in malaria and sepsis.

Box 1. Similarities between Severe Malaria and Septic Shock

In this review, GC and HPA axis function are compared between severe malaria and septic shock, because both conditions present a number of important similarities. Both are characterized by potent inflammatory responses (including increased cytokines, e.g., TNF-α), endothelial activation and vascular permeabilization, increased GC levels, coagulopathy, and a number of organ-specific complications including damage to the brain, lungs, kidneys, and liver. Cardiovascular collapse with hypotension and hypovolemia are cardinal features of septic shock and are also present in a subset of SM patients ('algid malaria'). Metabolic abnormalities, including hyperlactatemia and hyper- or hypoglycemia are also common in both diseases. Some important differences between severe malaria and septic shock relate to the etiology. Malaria-infected erythrocytes cytoadhere to the vascular endothelium and thereby directly cause vascular obstruction, which is thought to be one of the main pathogenic mechanisms. The pathogenesis of septic shock is rather related to the potent activation of inflammatory responses through direct stimulation of Toll-like receptors (TLRs) by bacterial products such as LPS. Malaria parasites are less potent activators of TLRs, although some components, for example, malarial glycosylphosphatidylinositol anchors, also activate TLRs and inflammation is also involved in SM. Furthermore, both conditions might co-occur, since malaria infection also predisposes to bacteremia, for example, with non-typhoid *Salmonella*.

Indeed, the **adrenal gland** is required to survive both sepsis and malaria, and dexamethasone treatment reverses the effect of **adrenalectomy** in both conditions [41–47].

In sepsis, among the adrenal hormones, GCs are essential mediators of tolerance. **Hypophysectomy** increases mortality from lipopolysaccharide (LPS)-induced shock [45]. When only the adrenal medulla was surgically removed, mortality from sepsis was unaffected in contrast to observations after complete adrenalectomy [48]. Also, the nonselective inhibitor of the GR, mifepristone (RU486), reduces survival in sepsis or renders the endotoxin-resistant TLR4-mutant C3H/HeJ mice sensitive to endotoxin [49,50]. Similarly, the SPRET/Ei mice that are resistant to a lethal dose of LPS, were sensitized to LPS by RU486 or adrenalectomy [51]. The LPS-resistant phenotype of SPRET/Ei mice is attributed to higher GR expression, a basal overactivation of the HPA axis and higher levels of the glucocorticoid-induced leucine zipper (GILZ) [51,52]. Similarly, GR overexpression enhances the resistance to endotoxic shock [53]. Moreover, dimerization of the GR is required to mediate survival after cecal ligation and puncture (CLP) and LPS-induced sepsis [54].

In contrast to data in sepsis, the functional role of GCs in malaria has received little attention. The increased levels of corticosterone in murine models of malaria correlated with parasitemia and severity of infection (Table S2). It was shown in the 1980s that in *Plasmodium berghei* K173-infected immunized Swiss mice, pregnancy-associated increases in corticosterone levels caused a loss of malarial immunity and more recrudescences. Even before that, two limited studies reported that adrenalectomy reduced survival in malaria, though no mechanisms were explored (references in Table S2).

In light of the delicate balance in immune and metabolic responses during malaria and the regulation of both processes by endogenous GCs, our group investigated the role of endogenous GCs in experimental malaria. The GC-reactivating enzyme, 11β-HSD1, modulates parasitemia, clinical disease score and plasma cytokine levels, depending on the parasite strain, but is not crucial for survival [55]. Knock-out of the 11β-HSD1 gene specifically abolishes the conversion of inactive GCs into their active forms in peripheral cells and tissues. It also results in a decreased negative feedback to the HPA axis and a subsequent increased adrenal production of GCs, leading to maintained or even elevated levels of circulating active corticosterone, hence explaining the mild phenotype [26,56,57].

In contrast, adrenalectomy drastically abrogates the induction of GCs upon stress. The effects of adrenalectomy were studied in four distinct mouse models of malaria [47]. Adrenal hormones were found to confer disease tolerance in malaria, since they protect against early death without affecting parasitemia. Treatment with a synthetic GC (dexamethasone) prevented lethality, strongly suggesting GCs as the main tolerance-mediating adrenal hormones, although the contribution of other adrenal hormones (e.g., aldosterone and/or catecholamines) cannot be ruled out. Interestingly, plasma GC levels were recently found to be associated with tolerance to malaria and other haemosporidian parasites in a wild bird population, suggesting conservation of this tolerance mechanism throughout evolutionary phyla [38].

Homeostatic Properties of Endogenous GCs during Infection

Endogenous GCs have many homeostatic properties that are essential to survive stressful conditions, such as a severe systemic infection. They promote survival via anti-inflammatory, gluconeogenic, and vascular effects (Figure 1).

Anti-inflammatory Functions

A functional GR suppresses inflammation within multiple or specific cell types, thereby contributing to survival from infection. Lethality after adrenalectomy during endotoxemia or malaria is accompanied by elevated levels of cytokines in the circulation and brain [45,47,58–60]. Full GR dimerization abilities are required for survival from CLP- and LPS-induced sepsis via downregulation of IL-1β in macrophages [54]. GC-mediated inhibition of p38 mitogen-activated protein kinase (MAPK) and upregulation of sphingosine kinase 1 (Sphk1) in macrophages are also required to suppress LPS-induced inflammation and lethality [61,62]. Knockout of the endothelial GR in septic mice increases mortality,

concomitantly with elevated circulating TNF-α and IL-6 levels [63]. However, this cannot be unambiguously interpreted since the Tie1 promotor, used to generate these mice, is also expressed in hematopoietic cells [64]. Furthermore, hepatic GR prevents mortality in septic mice via the inhibition of hepatic inflammation [63,65]. Dendritic cell (DC)-specific deletion of the GR rendered mice highly susceptible to LPS-induced septic shock, with increased inflammatory cytokines, hypothermia, and mortality [66]. The protective effect of GCs appeared mediated via suppression of IL-12 production by $CD8^+$ DCs, which is also essential to promote tolerance to subsequent challenges. In natural killer (NK) cells, GCs inhibit interferon (IFN)-γ and induce programmed cell death protein-1 (PD-1) expression to promote tolerance to LPS and to viral infections [67,68]. Overall, these studies indicate that endogenous GC signaling through the GR is essential to avoid exaggerated inflammation upon infectious stimuli. In malaria, the balance between the immune system and parasite growth and immune-evasion is critical and dictates whether the host survives [2]. This balance is determined by pro- and anti-inflammatory cytokines such as IL-12, IFN-γ, and IL-10, and inhibitory receptors such as PD-1. Conceivably, GCs appear crucial to maintain a balanced host response upon malaria infection. This is corroborated by the increased inflammation in malaria-infected adrenalectomized (Adx) mice [47].

Glucose Homeostasis

Importantly, GCs support gluconeogenesis. Besides stress-induced hyperglycemia, also spontaneous hypoglycemia occurs in sepsis and is associated with a higher mortality compared with iatrogenic hypoglycemia that results from intensive insulin therapy [69,70]. In early studies in septic mice, it is reported that an initial hyperglycemic state is followed by hypoglycemia [71]. Results from old studies in mice indicate that endotoxemia reduces liver **glycogen** stores and glycogen synthase activity and lowers the activities of gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase, fructose-1,6-biphosphatase, and glucose-6-phosphatase [71–75]. In this already highly challenged metabolic state, adrenalectomy leads to severe lethal hypoglycemia [48,71]. Witek-Janusek *et al.* reported that removal of the adrenal medulla exacerbated the hypoglycemia seen in normal endotoxin-treated rats. However, this was not as pronounced as in Adx rats, in which severe hypoglycemia coincided with hyperlactacidemia and depletion of liver glycogen [48]. Inhibition of hepatic GR with short hairpin RNA blunted the hyperglycemic stress response after induction of sepsis in mice [65]. Importantly, both hyper- and hypoglycemia occur frequently in severe malaria patients, with hypoglycemia associated with a poor outcome [3,76]. Exhaustion of glycogen stores and insufficient gluconeogenesis may thus be a prominent cause of the observed hypoglycemia, and this is further supported by the finding that fasting and infection-induced anorexia enhance the risk of hypoglycemia in malaria [3,5]. Our preclinical data suggest that adrenal hormones, and most likely GCs, are critical regulators of glucose homeostasis in malaria, since adrenalectomy results in lethal hypoglycemia and hepatic glycogen exhaustion in malaria mouse models [47]. Glucagon levels were in line with a normal counter-regulatory increase, whereas the transcription of hepatic gluconeogenic enzymes remained unaltered in infected Adx mice. The marked hypoglycemia was not prevented or reversed by glucose administration, TNF-α neutralization, or administration of clonidine, an α2-adrenergic agonist, which potently inhibits pancreatic insulin release [47]. In contrast, treatment with dexamethasone prevented the hypoglycemia, lowered cerebral cytokine expression, and significantly increased survival rates. Interestingly, this was not accompanied by the induction of gluconeogenic enzyme expression, suggesting that dexamethasone may mediate its protective effect mainly via the inhibition of excessive inflammation [47].

Vascular Effects

Adrenal hormones co-regulate the cardiovascular response, a phenomenon that possibly plays a crucial role in the **vasopressor** function during malaria. Cortisol enhances the vasoactive tone via the retention of intravascular fluid and stimulation of ionotropic and vasopressor responses to catecholamines and angiotensin II [21]. Sepsis is often characterized by a decreased response to catecholamines. This is thought to be due to desensitization or downregulation of the catecholamine receptor, which can be prevented by GCs [77]. Studies in Adx rodents, including complementation by dexamethasone, supported the essential role of GCs in controlling the vasopressor response during sepsis [78–80]. Adrenal hormones thus mediate additional tolerance to LPS by preventing severe

circulatory shock, characterized by the fall in blood pressure and vascular hyporeactivity to catecholamines. Several mechanisms seem to explain this protective effect by adrenal hormones, including an inhibition of nitric oxide (NO) synthesis and cyclooxygenase, rapid potentiation of catecholamine effects on mesenteric arteries, and induction of glutamine synthase, which indirectly maintains nitrogen homeostasis [78–82]. In addition, endothelial deletion of the GR coincides with more hemodynamic instability, elevated NO levels, and increased mortality after LPS administration [63]. In malaria, hypovolemia is common, and hypotension ('algid malaria') occurs in a proportion of patients [83]. Interestingly, in one study, low cortisol levels were found in hypotensive malaria patients [84]. GCs may thus protect malaria patients against hemodynamic instability, but further studies are required. Importantly, extensive endothelial activation is observed in malaria, often with increased barrier dysfunction and edema [85]. GCs have potent protective effects on endothelial cells by decreasing the expression of inflammation-related proteins and by increasing junctional molecules, thereby preserving the barrier function of the endothelium [86]. This suggests that endogenous GCs might be important to limit the endothelial damage in malaria, although the induction of glucocorticoid resistance by parasite products and cytokines may interfere with this protective effect [87].

Does a Dysfunctional HPA Axis Contribute to Disease Severity in Human Malaria?

Although critically ill patients mostly show a pronounced rise in cortisol, some patients seemingly have insufficient cortisol available to cope with high illness-related stress, denoted as critical illness-related corticosteroid insufficiency (CIRCI; previously labelled as relative adrenal insufficiency) (Box 2) [88–90].

Several older studies investigated the HPA axis in malaria patients, and the data are summarized in Table S1. In both UM and SM, mean cortisol levels appeared increased but ACTH remained within or below the control range. This is consistent with reduced cortisol elimination rate, as measured in

Box 2. Critical Illness-Related Corticosteroid Insufficiency (CIRCI), a Controversy

As malaria shares important characteristics with critical illness, particularly with sepsis, insights into the functioning of the HPA axis in critically ill patients may guide further research and advance insight into the field of malaria. However, there is still a lot of controversy surrounding HPA axis (dys)function in critical illness, and recent studies have challenged classical dogmas [89,90,99].

Critical illness is a condition of extreme physical and inflammatory stress in which cortisol levels rise proportionately with the severity of illness. This rise is considered vital to avoid shock and organ failure, to combat infections, and to repair tissue damage. The high cortisol levels were long assumed to result from a several-fold increase in ACTH-driven cortisol production. However, ACTH rapidly decreases, and recent evidence showed that the cortisol production rate is not, or only moderately, increased. Instead, cortisol metabolism appeared strongly decreased, largely explaining the hypercortisolemia.

In certain patients, particularly the sickest (e.g., with septic shock), high amounts of cortisol produced by a maximally activated adrenal cortex seemingly may not be large enough to cope with the severe stress of the illness, denoted as 'critical illness-related corticosteroid insufficiency' (CIRCI, previously labeled 'relative adrenal insufficiency'). An abnormally low total cortisol response to an ACTH stimulation test has been suggested to diagnose CIRCI and to identify patients who would benefit from hydrocortisone treatment in a so-called stress dose of approximately 200 mg/day. However, this concept appeared problematic. First, the ACTH stimulation test proved unreliable for assessing adrenocortical integrity or functional reserve. Indeed, a low total cortisol response to ACTH was shown to result from an increased cortisol distribution volume and low levels of cortisol-binding proteins, whereas free cortisol responses were normal or even higher than normal. Second, advised stress doses of hydrocortisone, equivalent to a six to ten fold increased cortisol production, do not consider the five to eight fold increased half-life of cortisol in critical illness and thus are probably too high, possibly increasing central adrenocortical suppression via feedback inhibition. The long-term safety for physical and neurocognitive functioning of such doses has not been proven. Third, treatment of septic shock patients with stress doses of hydrocortisone did not show a uniform survival benefit, although time to shock reversal, and weaning from mechanical ventilation, was mostly shortened. Clearly, careful investigation of these issues is needed. Also in malaria, these issues may play a crucial role and may be different for the specific complications of malaria.

SM patients [91]. In UM, both the **metyrapone suppression test** and the **dexamethasone suppression test** indicated a normal pituitary response, suggestive of an intact HPA axis [92,93]. In contrast, a **CRH stimulation test** revealed a suppressed pituitary response with low ACTH secretion in SM patients, which is indicative of a suboptimal HPA axis function [91]. Furthermore, the finding that cortisol is not increased in all SM patients [84,91] does suggest that CIRCI may occur in a subset of SM patients, possibly related to specific complications. As suggested by mouse models of malaria, disturbances in the HPA axis response might cause a loss of tolerance and the development of severe hypoglycemia and hyperinflammation in malaria. Whether this occurs in malaria patients and whether such patients might benefit from GC therapy to restore homeostasis requires further investigation.

Importantly, two clinical trials in the 1980s failed to show clinical benefit of GCs for patients with CM (Table S1). During the first trial in Thailand by Warrell *et al.*, 50 *P. falciparum*-infected patients with comatose CM were administered quinine and dexamethasone [2 mg/kg; intravenously (IV)] [94]. Dexamethasone had no effect on overall survival, and coma was even prolonged in some survivors. In the second, smaller study in Indonesia, Hoffman *et al.* used quinine and a higher dosage of dexamethasone (11.4 mg/kg; IV) in 18 CM patients and confirmed the lack of benefit, but did not detect deleterious effects [95]. Although Warrell *et al.* stated that complications such as pneumonia and gastrointestinal bleeding occurred more often in treated patients, a meta-analysis of both trials did not show significant differences [96]. Important to note is that, in both trials, all patients were treated with the antimalarial drug quinine. Quinine is known to induce hypoglycemia by insulin secretion, which may have masked the potential positive metabolic effects of dexamethasone [97,98].

Despite the apparent failure of dexamethasone to help patients with CM, one of the most fulminant complications, the therapeutic impact on larger patient numbers and other complications that have a broader therapeutic window remains unknown. With the caveat in mind that differences in pathophysiology between mice and patients cannot be excluded, it is important to note that GCs have beneficial effects against malaria-associated pathologies in mice (Table S2). Early dexamethasone treatment (before neurological symptoms appear) protected mice from lethal CM, inhibited hypothermia and pathological changes in various organs (brain, liver, lung, spleen, kidney) and reduced vascular permeability. Administration of a liposome-encapsulated formulation of the GC prodrug β-methasone hemisuccinate (BMS) upon *Pb*ANKA infection, reduced the toxicity and increased the efficacy compared with free BMS. It prevented CM and lowered edema, hemorrhages, and mRNA expression of IFN-γ, TNF-α, CCL2, CCL5, CXCL9, and intercellular adhesion molecule 1 (ICAM-1). Also, a decreased activation of microglia and astrocytes was found. In a murine model of MA-ARDS (*Pb*NK65-infected C57BL/6 mice), high doses of dexamethasone blocked the lung pathology, even when administered after appearance of the complication. This was paralleled by reduced pulmonary leukocyte accumulation and expression of IFN-γ and CCL2 (references in Table S2).

Overall, limited indications suggest that HPA axis dysfunctionality may occur in a subset of SM patients. More research is needed to define this subset, to evaluate whether it might be possible to translate the promising findings on GC treatment of experimental murine malaria into patients.

Concluding Remarks

GCs have pleiotropic activities on almost all cell types and are increased in sepsis and malaria. Overall, the essential roles of GCs for disease tolerance and survival during both malaria and sepsis most probably involve a balanced combination of their anti-inflammatory, glucometabolic, and vascular effects. Disruption of the HPA axis in murine malaria models results in increased inflammation and lethal hypoglycemia, and this can be rescued by exogenous GC treatment [47]. Treatment with dexamethasone may thus improve survival in the case of a failing HPA axis. However, translation to the human patient setting may be more complex than one assumes, considering the conflicting results and controversy that go along with GC treatment of CIRCI patients. Limited data suggest that possible dysfunctions of the HPA axis might occur in malaria patients, and that this may contribute

Outstanding Questions

Do aldosterone and/or catecholamines contribute to the tolerance in malaria by enhancing the metabolic and anti-inflammatory effects of GCs?

Do GCs limit endothelial damage and protect from hemodynamic instability in malaria?

Does corticosteroid insufficiency occur in malaria patients?

Does corticosteroid insufficiency contribute to severity or specific complications in malaria?

Can GC therapy be beneficial for a subset of patients with severe malaria and corticosteroid insufficiency?

to severity and/or specific complications, but further documentation is required (see Outstanding Questions). Although the failed clinical trials of dexamethasone against CM in the past have decreased the interest in GCs in malaria, more research in this field is warranted. More in-depth studies of patient subpopulations with HPA dysfunctions might possibly clarify whether some SM patients may benefit from GC therapy.

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