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Mini-Review

Corticosteroid-binding globulin (CBG) in central, systemic and cellular stress response

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ABSTRACT

Regulation of central and systemic stress response is in part controlled by the hypothalamo-pituitary-adrenal (HPA) axis. Adrenal steroids cross the blood brain barrier to act on the brain through nuclear receptors. In recent studies we described the intrinsic expression of corticosteroid-binding globulin (CBG) in rat and human brains. It is likely that known rapid effects of glucocorticoids (GCs) are mediated by non-genomic actions involving intrinsic binding globulins. CBG enhances bioavailability of systemic GCs thus increasing anti-inflammatory capacity and glucose utilization. A membrane receptor for CBG/GC has been postulated which in part could account for known non-genomic GC effects including the blockade of cytokine secretion. Intracellular CBG may be important for cytoplasmic steroid transport, for binding of GCs that are synthesized in the mitochondrial compartment, and for delivering GCs to cytosolic glucocorticoid receptors (GCR). CBG may be part of a complex cascade of central, systemic, membrane-based, cytoplasmic, mitochondrial, and nuclear events.

KEYWORDS: hypothalamus-pituitary-adrenal axis, stress response, inflammation, corticosteroid-binding globulin

INTRODUCTION

Stress responses are important physiological and behavioral mechanisms necessary for survival under changing environmental conditions. Stressful stimuli are relayed to the brain by either cognitive or visceral inputs. In response the limbic system activates central stress factors including the neurohypophyseal peptides vasopressin (VP), oxytocin (OT) and the adenohypophyseal factor corticotropin releasing hormone (CRH). All of them enter the pituitary portal circulation in the median eminence to activate corticotrophs in the anterior pituitary lobe, which liberate adrenocorticotropin (ACTH) into the blood stream [1]. Adrenocortical steroid hormones (especially glucocorticoids, GCs) depend almost exclusively on systemic ACTH. Circadian rhythm is linked to changing systemic GC levels [2]. Affective disorders are thought to be triggered by a dysregulated HPA axis, reflected by permanently increased CRH, ACTH and GC levels [3]. GCs are capable of crossing the blood brain barrier due to their lipophilic nature. Circulating GCs are peripheral mediators of central functions [4]. The distribution of glucocorticoid receptors (GCR) throughout the central nervous system has been extensively studied by steroid autoradiography and by immunocytochemistry some time ago [5]. Evidence for GC targets has been found in the cerebral cortex, the hippocampus, amygdala, brain stem, piriform cortex, basal ganglia and spinal cord. Clearly, neurons in many portions of the limbic system seem to express GCR [5]. The most obvious GC effects are on the hypothalamus: GCs are known to regulate the hypothalamo-pituitary-adrenal (HPA) axis in a dose-dependent manner as positive or negative feedback [4]. Interestingly GCR are expressed in the peptidergic hypothalamic neurons only to a rather small extent [6]. GCs have a variety of effects on their target cells and the concept of

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steroids acting solely *via* nuclear receptors had to be expanded [7]. Briefly, cytosolic GCR is dimerized upon binding to GCs to be translocated into the nucleus where GCR-GC acts as a transcription factor. In addition to their genomic actions *via* nuclear receptors, steroid hormones have rapid effects on the membrane level, most likely triggering specific cellular signaling pathways. These seem to be mediated through a novel class of receptors [8], which involve extracellular steroid-binding globulins [9]. Such non-genomic GC effects are probably linked to corticosteroid-binding globulin (CBG) [10].

CBG in brain, pituitary, and in the olfactory system

Corticosteroid-binding globulin (CBG) is a highly conserved glycoprotein with an approximate size of 50 kDa, expressed in all mammalian species including humans [11]. Over 95% of systemic GCs are bound to CBG, which serves as a steroid buffer thus enhancing their bioavailability [12]. The affinity of CBG is highest for cortisol and corticosterone, followed by progesterone. Its affinity is low for mineralocorticoids [8]. Synthetic GC agonists like dexamethasone or betamethasone are bound by CBG only to a very small extent. CBG-encoding DNA is located on human chromosome 14, and its sequence and molecular detail have been studied extensively [12, 13]. The greatest CBG amounts are expressed in liver controlled by systemic estrogen and glucocorticoid levels [14] but also by cytokines and monoamines. CBG is expressed in other organs including adenohypophysis, adrenals, gonads and heart [15]. We observed CBG expression in various brain regions [16, 17] in certain neurons and in glial cells by immunocytochemistry, *in situ* hybridization, and reverse transcriptase polymerase chain reaction (RT-PCR) [18]. There is only a relatively small overlap between the localization of CBG and GCR in the central nervous system [6, 19]. The most abundant localization of CBG is in hypothalamus and in parts of the limbic system e.g. the hippocampus [20]. In hypothalamus, CBG is mainly found in magnocellular perikarya of the paraventricular and supraoptic nuclei, in part co-localized with VP and OT. Magnocellular neurons are mostly devoid of nuclear GCR [6, 21]. Nevertheless both OT and VP have been shown to respond to altered systemic GC levels and to be closely involved in central and systemic stress responses [22]. Immunocytochemistry revealed that magnocellular axonal varicosities in the median eminence and secretory nerve endings in the neurohypophysis showed in part double staining of CBG with either VP or OT. Immunoelectron microscopy revealed colocalization of sex hormone-binding globulin SHBG with OT indicating that steroid-binding globulins of hypothalamic origin are subject to axonal transport and terminal release in a neurohormone-like fashion [23]. The functional importance of neurohypophyseal CBG is yet to be determined. In light of the vast amounts of liver borne systemic CBG, secretion of hypothalamic CBG into the blood stream seems unlikely. Perhaps CBG of the hypothalamo-neurohypophyseal system serves to facilitate local GC binding on magnocellular nerve terminals to modulate VP and OT release. Both peptides are known to play important roles in systemic stress response by increasing blood pressure through increased vasotonus and increased renal water retention [22]. Central stress response most likely involves rapid steroid effects, which have been suspected to be among the functions mediated by CBG. CBG knockout mice exhibit dramatically altered endocrine and behavioral stress responses [24]. Such animals displayed enhanced despair-like behavior and altered memory response upon specific stress as compared with controls. It seems possible that CBG plays an important role in affective disorders in humans, given the fact that such conditions are linked to an upregulated HPA axis [25].

In hippocampus, a region known to be affected by changing GC levels, CBG is found in pyramidal and in non-pyramidal cells of the CA 1, the CA 2, and CA 3 region, while the CA 4 region and the dentate gyrus are mostly devoid of CBG. CA 1 and the dentate gyrus have the highest concentration of nuclear GCR [26]. This differential distribution seems to be malleable to functional status. In rats afflicted with acute sepsis all portions of the hippocampus show extensive nuclear GCR immunostaining while CBG has become almost undetectable [27]. Therefore, it seems that CBG and GCR act separately to mediate GC effects in different hippocampal areas and that this relationship can change with immune function and/or stress states.

A small portion of glial cells within the motor and sensory cortices shows CBG immunostaining.

These cells were mostly astrocytes as determined by glial fibrillary acidic protein (GFAP) double staining, and some oligodendrocytes as characterized by CNPase (2′,3′-cyclic nucleotide-3′-phosphodiesterase) immunofluorescence [17]. In the glioblastoma cell line 1321N1, CBG was only partly co-localized with GCR [18], suggesting again that CBG can have effects in brain cells that are devoid of GCR. CBG secretion was observed in these cells upon GC treatment, supporting the idea that "non-genomic" rapid effects of GC in brain may be mediated through CBG and its putative membrane receptor [8]. The presence of CBG in oligodendrocytes raises the question about its potential involvement in myelinogenesis. The well documented dual role of GCs in the maturation of oligodendrocytes and formation of myelin in patients with multiple sclerosis [28] might be a further indication for a possible dysregulation of intracellular CBG expression in patients with this disease. Moreover, CBG may serve as a neurotrophic factor during brain development since synapse formation and myelination are altered by prenatal treatment with GC agonists [29].

Numerous endocrine cells in the anterior pituitary lobe show CBG immunostaining. They also contain CBG-encoding mRNA, suggesting intrinsic CBG expression. Interestingly, only a small percentage of CBG-containing cells in the anterior pituitary were corticotrophs. Most of the CBG cells in pituitary are prolactin-producing cells or gonadotrophs, as determined by double immunostaining [16]. The functional importance of pituitary CBG is unclear. CBG secreted in a paracrine fashion within the anterior lobe could aid interstitial GC buffering and transport to CBG/GC responsive membrane sites on endocrine cells to facilitate known rapid effects of the steroid hormones. This may be especially true for corticotrophs, which have to control ACTH liberation quickly upon elevated serum GC levels. Although many endocrine cells in the anterior lobe contain nuclear steroid receptors [1], genomic GC actions on pituitary corticotrophs may be inadequate to facilitate ACTH release, which clearly is a function of the cell membrane and not under direct control of the genome. Systemic GCs regulate ACTH and CRH release *via* feedback loops. Again these are rapid, nongenomic steroid effects involving a respective membrane receptor.

Sensory cells within the olfactory epithelium, in the vomeronasal organ (VNO), and secretory cells of the olfactory glands express significant amounts of CBG [30]. Consequently, nasal secretions also contain CBG. Experiments in rodents indicate that volatile GCs and their metabolites stimulate sensory cells in the VNO [31]. Aerosolic GCs may serve as pheromones important in the regulation of fear, dominance behavior, and social hierarchies. Steroid hormones are known to be among the most potent olfactory ligands. Clearly a pheromone should function rapidly in order to induce efficient behavioral responses. GC actions through classic GCR are most likely inefficient in this context since they are too slow. Again pheromonal CBG/GC may act on olfactory sensory neurons through the above-mentioned membrane effects. The CBG-deficient mouse model showed dramatic decrements in social behaviors upon olfactory stimuli [24, 32].

Inflammation and stress response

GCs are widely used for the treatment of various conditions linked to inflammation ranging from allergies and asthma to autoimmune and rheumatic diseases. Naturally a hormone that provides immediate symptomatic relief for a vast number of ailments is quite attractive in many clinical fields. Inflammation is probably among the most common chronic systemic stressors [33, 34]. It is characterized by liberation of cytokines from cells of the immune system in response to a number of stimuli including monoamines, immunoglobulins, and bacterial or viral toxins [35]. Inflammatory stress and subsequent activation of the immune system is vital. However extended inflammation will affect health and therefore requires counteractive mechanisms. This is especially true if various stressors accumulate. High plasma levels of pro-inflammatory cytokines activate HPA axis and increase systemic GCs [36]. Under conditions wherein an animal is acutely threatened, all kinds of homeostatic processes are shut down in favor of energetic processes that increase muscle action and thus allow for escape from harm. Under such stressful conditions, GCs serve to shut down inflammatory processes by rapidly suppressing cytokine release [37]. CBG is thought to support anti-inflammatory GC effects by buffering systemic steroid levels. However, during chronic inflammation

both GC and CBG levels are low [38], such that inflammation may get out of control because there is less GC available to hold these processes in check. Use of GC agonists as therapeutic remedies seeks to increase overall anti-inflammatory capacity which is thought to be provided only by free GCs. Hence GC is applied in doses high enough to exceed buffering capacity of CBG. GC effects on leucocytes are instant and therefore unlikely to be mediated through nuclear receptors. The role of CBG in the anti-inflammatory actions of GCs is still far from clarification. Most certainly there is a complex cascade of events initiated by the liberation of cytokines to trigger cellular and hormonal immune responses, both locally and systemically. CBG may mediate all or part of these effects because it increases the bioavailability of GCs. Adrenal steroid secretion is known to follow a diurnal pattern in healthy subjects. This is controlled by the HPA axis but not paralleled by hepatic CBG secretion, which is constant under normal conditions [2]. Systemic GC levels rise in the morning and fall at night to reach minimum levels during sleep [39]. This results in a nocturnal rise in cytokine levels (especially IL2, IL6 and TNF alpha) [40]. During sleep, the body temperature increases while cardiovascular activity and muscle tonus decrease. In terms of cytokine release sleep can be considered a circadian physiological state of inflammation. This increased immune response may be essential for maintaining cellular homeostasis, and removal of degenerated cells and of pathogens. This may be among the reasons why rest and sleep are beneficial for recovery from ailments.

The cellular and molecular mechanisms of GCs protective effects in systemic inflammation are yet to be determined. GCs block cytokine liberation from leukocytes *via* rapid, most likely membrane-mediated effects [41]. Interestingly, most lymphocytes are devoid of nuclear GCR. It is therefore unlikely that anti-inflammatory GC effects follow the classic genomic pathway. In addition these effects are fast. Cytokine secretion *via* exocytosis is clearly a membrane-associated event. Hence membrane receptors are more likely to be involved than transcription factors.

Hepatic CBG expression is increased by TNFα and IL6 [38, 41]. This may result in a temporary pro inflammatory effect of CBG since it buffers free GCs, rendering them ineffective for blocking exocytosis. Many leukocytes, including neutrophils, express in their membranes a specific elastase (Neutrophil elastase, N-el), which lowers CBG affinity for GCs, thus liberating the steroid from its binding globulin [42]. This will then allow for direct GC effects on the target cell membrane and may also control entry of GCs into the cytoplasm. So CBG/GC complexes have most likely anti inflammatory properties. This dual role of CBG may be quite important for limiting inflammation within physiological boundaries. We could show that neurohypophyseal CBG as well as OT is depleted in septic animals [27]. The proportions of free GCs versus GCs bound to CBG and their respective levels are vital in this context. They are known to be altered in acute and in chronic inflammation [43, 44].

CBG in the heart

Chronically elevated GC levels are known to induce reactions other than immunomodulation. Symptoms include Cushing's disease, metabolic syndrome, insomnia or depression. Such GC effects have to be considered in any long term therapeutic setting. GCs seem to cause apoptotic cell death in neurons of the hippocampus and in the adrenal cortex [45, 46, 47]. Again the cellular and molecular events associated with GC toxicity are mostly unknown. Cells of the myocardium seem to be particularly vulnerable. This is especially true for the cardiac Purkinje fibers, which represent specialized cardiomyocytes, capable of electrical excitation. The cardiac conduction system is composed of Purkinje fibers. Arrhythmia and cardiac failure has been shown to be associated with chronically elevated stress levels [48, 49]. Extreme stress can cause cardiac damage sometimes followed by immediate death. This is known as Tako Tsubu cardiomyopathy or broken heart syndrome. Symptoms are similar to that of a heart attack but without damage to the vasculature [50]. Instead systemic levels of adrenal stress hormones epinephrine, norepinephrine and glucocorticoids are extremely high [51]. Extended high systemic GC levels have been suspected to be involved in myocardial damage although cardiomyocytes are devoid of nuclear GCR. Cardiomyocytes express however nuclear mineralocorticoid receptors (MCR) which are known to respond to GCs in heart [52]. We could recently show that human myocardium expresses CBG.

Both CBG protein and the encoding transcripts have been detected using immunocytochemistry, *in situ* hybridization and using RT-PCR [53]. Myocardial CBG was in most cases co-expressed with N-el. Again, the highest amounts of N-el also seem to occur in Purkinje fibers [54], which are particularly sensitive to chronically elevated GC levels [15]. This suggests that both CBG and N-el are part of a cellular GC response system within the heart. Incidence of cardiac arrhythmia and atrial fibrillation correspond with chronically elevated systemic GC levels, long-term high-dose GC treatment and with chronic stress [55]. It is likely that myocardial N-el facilitates liberation of GCs from CBG also in myocardium to enhance glucose utilization in the metabolically challenged muscle cells. High doses of free GCs may induce cytotoxic effects also in heart. Amounts of N-el and CBG versus free GC in serum may therefore be valuable early prognostic indicators of various stress-associated cardiac ailments including atrial fibrillation.

Systemic versus oxidative stress

Biosynthesis and metabolisms of GCs is closely associated with mitochondrial membranes [56]. Furthermore GCs affect mitochondrial glucose utilization and respiratory chain thus increasing oxidative stress [57]. Free radicals that are generated during these processes (including reactive oxygen species, ROS) impair mitochondrial performance, ultimately leading to mitochondrial depletion and apoptotic cell death. The above mentioned GC toxicity is in part linked to mitochondria [58]. Intracellular corticosteroid-binding globulin seems to be of importance for transporting steroids through the cell membrane to cytoplasmic steroid receptors for translocation into the nucleus [7]. Cytoplasmic corticosteroid-binding globulin may also be important for transport and liberation of GCs. GC biosynthesis and metabolism is closely associated with mitochondrial membranes [59, 60]. Hence GCs and their binding globulins link the cascade of central, systemic and oxidative stress. “Stress axis” is actually “stress response axis” and consequently GCs (as well as adrenal monoamines) are stress response hormones.

The dose-response curve of hypothalamic neurons to changing GC levels does not seem to be linear: While small amounts of GCs stimulate hypothalamic and limbic neurons, large amounts generally inhibit these cells. GCs elevate serum glucose levels by stimulating gluconeogenesis in the liver but they also increase glucose utilization in mitochondria of numerous other cells [33]. Glycolysis is vital for mitochondrial functions including ATP production. Free radicals, which are generated upon these events have deleterious effects on mitochondrial performance [61]. Such GC effects are referred to as “GC toxicity”, which ultimately impair mitochondria [62]. Cellular and mitochondrial anti-oxidative capacity is therefore essential for cell survival. Chronic systemic stress, represented by a permanently activated HPA axis and elevated GC levels, results in increased levels of free radicals which cause oxidative stress. Loss of mitochondria eventually triggers apoptotic cell death. Intracellular CBG buffers GC thus diminishing oxidative stress. This is among the cellular responses to excessive metabolism which generated free radicals. Thus intracellular CBG also adds to cell’s anti-oxidative capacity.

CONCLUSIONS

The functional importance of CBG certainly exceeds that of a mere systemic steroid buffer. There are several roles for this binding globulin. Intrinsic expression in the central nervous system seems to be linked to central stress response since it is closely associated with the HPA axis, the posterior lobe peptides and the limbic system. Furthermore it is involved in binding pheromonal GCs in the olfactory system. CBG also seems to be important for systemic stress response. Its expression and liberation in liver is modulated by serum cytokines. Since CBG binds to GCs, it provides pro inflammatory functions. On the other hand CBG-GC complexes are likely anti inflammatory since N-el sequesters GCs from CBG to block cytokine release. This dual role may be important for modulation of inflammatory stress response. Systemic CBG buffers serum GCs thus increasing glucose utilization. Hence systemic stress response is also among the functional properties of CBG. All of these functions are fast and do not seem to involve genomic GC.

CBG is among the factors that link central, systemic, cellular, and mitochondrial stress responses (see sketch figure 1). GC target cells do not necessarily need to express nuclear GCR. Instead their membrane-

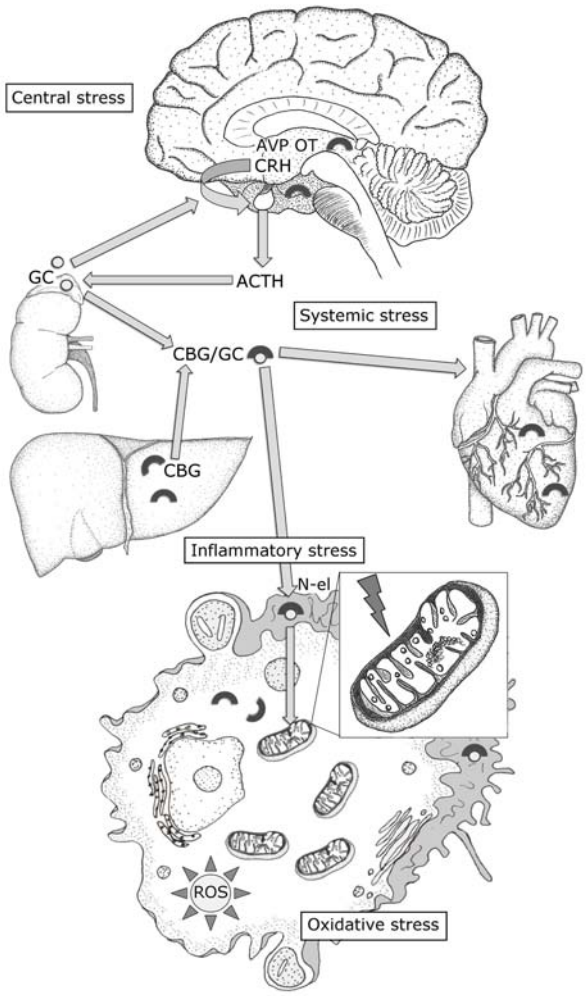

Figure 1. Cascade of central, systemic, inflammatory, and oxidative stress: stress responses are generated in the brain. The hypothalamus-pituitary-adrenal axis is activated through CRH and potentiated by OT and AVP. Pituitary ACTH stimulates adrenal GC release, which triggers liberation of hepatic CBG. CBG-GC complexes affect various organ systems including the cardiovascular system. On the cellular level GCs are liberated from CBG by membrane-based neutrophil elastase to block cytokine release and to stimulate glucose metabolism in mitochondria which enhances the generation of oxidative stress thus impairing mitochondrial function.

associated elastases aid in liberating GCs from CBG at the membrane level and it is likely that these effects are receptor mediated. A membrane receptor for CBG-GC has been postulated which in part could account for known rapid non-genomic GC [8] effects including the blockade of cytokine secretion. Intracellular CBG may be important for cytoplasmic steroid transport, for binding of GCs that are synthesized in the mitochondrial compartment, and for delivering GCs to cytosolic GCR. The transfer of GC-GCR complexes into the nucleus may also involve CBG [7, 9]. Hence CBG may be part of a complex cascade of systemic, interstitial (extracellular), membrane-based, cytoplasmic, mitochondrial, and nuclear events. Chances are that similar functional properties apply also for other specific steroid-binding globulins in various organs including heart and brain. There is an increasing body of evidence that this is true for sex hormone-binding globulin and for vitamin D-binding protein [9].

CONFLICT OF INTEREST STATEMENT

There is no conflict of interests to report.

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