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Corticosteroid-binding globulin: Modulating mechanisms of bioavailability of cortisol and its clinical implications

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Corticosteroid-binding globulin (CBG) is the principal transport protein of glucocorticoids. Approximately 80–90% of serum cortisol binds to CBG with high affinity and only about 5% of cortisol remain unbound and is considered biologically active. CBG seems to modulate and influence the bioavailability of cortisol to local tissues. In this review, we will discuss physicochemical properties of CBG and structure of CBG in the mechanisms of binding and release of cortisol. This review describes several factors affecting CBG functions, such as genetic factors or temperature. Furthermore, clinical implications of CBG abnormalities and the measurement of CBG and its use for assessment of free cortisol levels are described in this review.

Introduction

Corticosteroid-binding globulin (CBG) is the principal transport protein of glucocorticoids, mainly cortisol. Approximately 95% of secreted cortisol is bound to carrier proteins; 80–90% to CBG with high affinity and low capacity and 10–15% to albumin with low affinity and high capacity [1]. The remaining 5% of cortisol remain unbound and free to diffuse across cell membranes and bind to intracellular glucocorticoid and mineralocorticoid receptors. According to the traditional “free hormone

Abbreviations: CBG, corticosteroid-binding globulin; IL-6, Interleukin-6; PCOS, polycystic ovary syndrome; R-form, relaxed form; RCL, reactive center loop; S-form, stressed form; SERPIN, serine protease inhibitor.

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hypothesis" [2] unbound cortisol is considered biologically active. CBG has been extensively investigated in terms of its role as a carrier of corticosteroids. In addition, CBG acts as a buffered source of circulating cortisol as well as a modulator that will allow a varied release of cortisol to the tissues [3,4]. Mechanisms of binding and release of cortisol have been elucidated by recent crystal structure analyses [5–7]. The CBG-cortisol complex binds to the CBG-receptors on the cell membrane to induce an accumulation of cAMP as a secondary messenger in different cells [8–10].

In this review, we will discuss physicochemical properties of CBG, cortisol binding and release mechanisms from CBG, factors affecting CBG functions, measurement of CBG and its use for assessment of free cortisol levels, clinical implications and future research on CBG.

Physicochemical properties of CBG

CBG is a clade A member of the serine protease inhibitor (SERPIN) family encoded by SERPINA6 that comprises five exons. CBG is a monomeric glycoprotein and accounts for less than 0.05% of all serum proteins. CBG is secreted as a 383-amino-acid peptide after cleavage from a 22-amino-acid signal peptide and circulates strongly regulated at a concentration range from 30 to 52 pg/ml [11]. Whereas its molecular size determined by size exclusion chromatography or denaturing polyacrylamide gel electrophoresis ranged between 50 and 60 kDa, knowledge of its primary structure provided a precise molecular size of 42,646 Da [12]. About 30% of CBG mass is represented by N-linked oligosaccharide chains. CBG includes one steroid binding site, six N-glycosylation sites, and a reactive center loop that acts as a protease bait domain [13].

CBG is principally produced by hepatocytes in the liver [14]. It has been reported that CBG is also expressed by lung, kidney and testis [12] as well as during development of kidney and pancreas [15,16]. Extra-hepatic production of CBG appears to control the tissue availability of steroids locally rather than to contribute to plasma CBG levels systemically. The biological half-life of CBG has been determined to be about 5 days [17,18].

Cortisol binding and release mechanisms

CBG is known to bind cortisol with a one-to-one molar binding ratio [19,20] and binds corticosteroids in a surface pocket underlying the main β-sheet with an affinity constant of 33 nM [7].

The β-sheet expands as the molecule undergoes a conformational change from a high affinity stressed-form (S-form) to a low affinity relaxed-form (R-form), when the reactive centre loop is cleaved by proteases released from neutrophils at loci of inflammation. This S-to-R change in CBG results in a 10-fold decrease in its binding affinity for corticosteroids accompanying the insertion of the reactive centre loop into the body of the molecule. Consequently, cortisol is released from CBG at sites of inflammation [5] (Fig. 1).

Klieber et al. [6] proposed that helix D, which is in a helix-like conformation in intact CBG, could be involved in regulating hormone binding. Incorporation of the cleaved reactive centre loop into the central β-sheet was found to be accompanied by a partial unwinding of helix D [5]. The steroid-binding site of the cleaved human CBG adopts a configuration that closely resembles that of the uncleaved CBG. Recent crystallographic studies showed how the movement of the reactive loop allows a modulated and reversible release of cortisol from CBG. This finding supports the hypothesis that the variation in the hormone binding affinity results from equilibrated changes in the flexibility or plasticity of the binding pocket [5,7].

Factors affecting CBG functions

CBG plays a vital role as a circulating reservoir of cortisol in the circulation, leaving only about 5% of free cortisol. The concentration of free cortisol depends primarily on the binding activity and the concentration of CBG. Functions and synthesis of CBG vary with genetic factors, gender, temperature, glycosylation state, concomitant medications and physiological changes in body temperature.