Perspectives in Diabetes

Handicaps to Host Defense

Effects of Hyperglycemia on C3 and *Candida albicans*

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The hyperglycemic patient remains persistently at risk for infectious complications. Whether ascribable to diabetes mellitus, to the administration of glucocorticoids, or to the infusion of hyperalimentation fluids, hyperglycemia may impair several mechanisms of humoral host defense, including such varied neutrophil functions as adhesion, chemotaxis, and phagocytosis. In addition, binding of glucose to the biochemically active site of the third component of complement C3 inhibits the attachment of this protein to the microbial surface and thereby impairs opsonization. Last, several pathogens frequently encountered in hyperglycemic patients possess unique mechanisms of virulence that flourish in the hyperglycemic environment. Most notable in this regard is the yeast *Candida albicans*, which expresses a glucose-inducible protein that is structurally and functionally homologous to a complement receptor on mammalian phagocytes. This protein promotes adhesion in the yeast and subverts phagocytosis by the host. Thus, hyperglycemia serves as a central mechanism in the predisposition of hyperglycemic patients to infection. *Diabetes* 39:271–75, 1990

Despite the many recent advances in the treatment of diabetes mellitus, infection remains a leading cause of morbidity and mortality. Whether the diabetic patient displays an increased susceptibility to infection remains a source of controversy; however, there is abundant evidence that certain types of infections are peculiarly associated with the diabetic state. Among these are fungal infections such as rhino-oculocerebral mucormycosis, local and invasive forms of candidiasis, emphysematous infections of the biliary tree or urinary tract, and infections of the bones and soft tissues with various organisms, especially at sites of impaired vascular supply (1–3). Equally abundant is the evidence that several metabolic derangements in diabetes may impair a myriad of host defenses encompassing both humoral and cellular aspects (1,4,5). Nonetheless, a unifying explanation for the association of diabetes and infection has not appeared.

Patients with hyperglycemia alone even in the absence of other metabolic abnormalities are also at risk for infection; the organisms implicated are in many cases similar to those involved in infectious complications in the diabetic patient. For example, patients receiving parenteral hyperalimentation have been shown to be at increased risk for invasive fungal disease when compared with age- and sex-matched control subjects (6), whereas the administration of exogenous glucocorticoids to patients or laboratory animals is associated with an increased likelihood of candidal infection (7,8).

My perspective is that elevated plasma levels of glucose—even in the absence of other metabolic abnormalities—serve as a pivotal factor in the predisposition of hyperglycemic patients to infectious diseases both by impairing basic mechanisms of humoral host defense and by promoting microbial virulence. A comprehensive review of cellular immunity in the diabetic host or an extensive discussion of the participation of other factors such as insulin, β-hydroxybutyrate, or arachidonic acid metabolites in the response to infection is beyond the scope of this article. Instead, I focus on the mechanisms by which hyperglycemia impairs host defenses, including neutrophils and complement proteins, and promotes the virulence of organisms commonly encountered in infections in hyperglycemic patients.

EFFECTS ON NEUTROPHIL FUNCTION

Multiple investigations have established that the hyperglycemic environment handicaps neutrophil functions as diverse as adhesion, chemotaxis, phagocytosis, and intracellular killing (9–18). Moreover, the incubation of normal granulocytes in serum from untreated diabetic patients also reduces phagocytic function (19). Coupled with these func-

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tional impairments are metabolic defects associated with hyperglycemia, which include a decreased rate of glycolysis, the accumulation of glucose-6-phosphate and fructose-6-phosphate, and reduced synthesis of glycogen by the neutrophil (20–23). In vitro evidence from studies of neutrophil phagocytosis in diabetic animals and patients has demonstrated that phagocytic dysfunction can be corrected or at least substantially improved with control of plasma glucose (12,19). The results of these experiments lead to the hypothesis that the basis of impaired host defense in hyperglycemic diabetic patients is an abnormal interaction between glucose and plasma proteins rather than intrinsic defects in neutrophil function.

This hypothesis is further substantiated by reports that the degree of phagocytic impairment in diabetes correlates directly with the level of plasma glucose (24). Such defects can be reproduced in vitro by preincubating normal plasma with concentrations of D-glucose equivalent to 15 mM. In phagocytic assays, decreased uptake of the yeast *Candida guillermondii* was directly correlated with both the concentration of glucose and the duration of preincubation; identical concentrations of D-mannitol had no inhibitory effect. When yeasts were incubated in normal plasma, washed, and then incubated in diabetic plasma, phagocytosis by normal neutrophils was not depressed. These results suggest that the function of plasma opsonins is impaired by high concentrations of glucose.

GLYCOSYLATION OF C3

Previous experiments have shown that the covalent attachment of C3 to the microbial surface is the critical determinant of phagocytic recognition (25). We have therefore attempted to characterize the mechanisms by which glucose interferes with the attachment of C3, thereby impeding phagocytosis. This opsonic process is regulated by the internal thiolester bond of C3, which resides in a hydrophobic pocket in the C3d subdomain of the α-chain (26; Fig. 1, *shaded area*). As shown in the schematic diagram, the internal thiolester bond connects a sulfhydryl group of a cysteinyl residue with a reactive carbonyl group on an adjoining glutamyl residue (27,28). When complement is activated, the C3a fragment is enzymatically cleaved from the amino terminal of the α-chain. Concomitantly, a conformational change in the protein exposes the thiolester bond. The next 60 μs of the protein's half-life determine one of three possible interactions (Fig. 1, *bottom*). If, as most commonly occurs, water is the predominant element in the microenvironment, the glutamyl carbonyl binds water and forms a carboxylic acid rendering the protein incapable of further interaction; this is called hydrolytic inactivation. However, if free hydroxyl or amino groups are present in appropriate proximity and concentration, the glutamyl carbonyl effects a transesterification reaction by which C3b binds in ester linkage with hydroxyl groups or in amide linkage with amino acceptors (28).

Although this interaction has subsequently been demonstrated to be the basis for the opsonic attachment of C3b to carbohydrates or amino groups on the surfaces of organisms as diverse as *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Escherichia coli* (25,29), the covalent binding reaction was originally described in the fluid phase with 50-mM concentrations of small molecules such as the monosaccharides sucrose and D-glucosamine (28). There is thus abundant biochemical evidence that hexoses in appropriate concentrations may serve as acceptor sites for the covalent attachment of C3b via its reactive thiolester bond. Similar concentrations of glucose are readily achievable in the urine, and in extreme hyperglycemia, even in the bloodstream. Thus, based on biochemical studies, it is theoretically possible for C3 to attach covalently and irreversibly to glucose. When infection ensues in a hyperglycemic environment, glucose may compete with microorganisms for the attachment of C3 and thereby inhibit opsonization.

FUNCTIONAL CONSEQUENCES OF GLYCOSYLATION OF C3

The biochemical, hemolytic, and opsonic functions of glycosylated C3 have been explored in preliminary studies (30). When C3 was incubated in normal human plasma made either 5 or 50 mM in glucose, the hemolysis of rabbit erythrocytes (a process known to be mediated by the internal thiolester bond; 31) was significantly decreased after incubation of otherwise normal plasma with 50 mM (as opposed to 5 mM) glucose. To establish the mechanism underlying these observations, [^{14}C]glucose was incubated with normal human serum to achieve concentrations of 5 or 50 mM (equivalent to glucose concn 90 vs. 900 mg/dl, respectively). C3 was then isolated from plasma by affinity chromatography, and incorporation of glucose (mol glucose/mol C3) was determined by scintillation counting and absorption spectrophotometry. After 18 h at 37°C, 7.6 ± 6.7% of all C3 molecules in normal human serum were glycosylated in 5 mM glucose, and 27.2 ± 9.4% of C3 molecules were glycosylated after incubation with 50 mM glucose ($P < 0.02$). Under these conditions, [^{14}C]glucose was bound exclusively to the β-chain of C3 and not at the thiolester site in the α-chain as demonstrated by autofluorography. Thus, passive incubation of C3 with glucose results in glycosylation of the C3 β-chain. Glycosylation is of negligible degree in euglycemic plasma but is significantly increased by hyperglycemia.

However, when microorganisms were added to plasma to simulate infection and activate complement, there were several significant differences. First, glycosylation of C3 under these conditions was greatly increased: in the presence of 5 mM glucose, 15.1 ± 7.2% of all C3 molecules were glycosylated, whereas 59.2 ± 5.8% of C3 molecules were glycosylated in the presence of 50 mM glucose ($P < 0.0001$). Analysis by autofluorography demonstrated that under conditions of complement activation glycosylation occurred not only on the β-chain but also on the α-chain fragments that contained the C3-thiolester bond. Thus, disruption of the C3-thiolester bond during complement activation resulted in increased glycosylation of C3 attributable to the covalent attachment of glucose at the thiolester site.

Because glucose serves as an alternative acceptor for C3, the presence of high concentrations of glucose may divert C3 from the microbial surface and thereby impair opsonization. This hypothesis was confirmed by incubating radiolabeled C3 in plasma made 5 or 50 mM in glucose. Opsonic deposition of C3b on *Candida albicans* was significantly decreased under hyperglycemic conditions ($P < 0.02$). By examining the first phase of opsonophago-

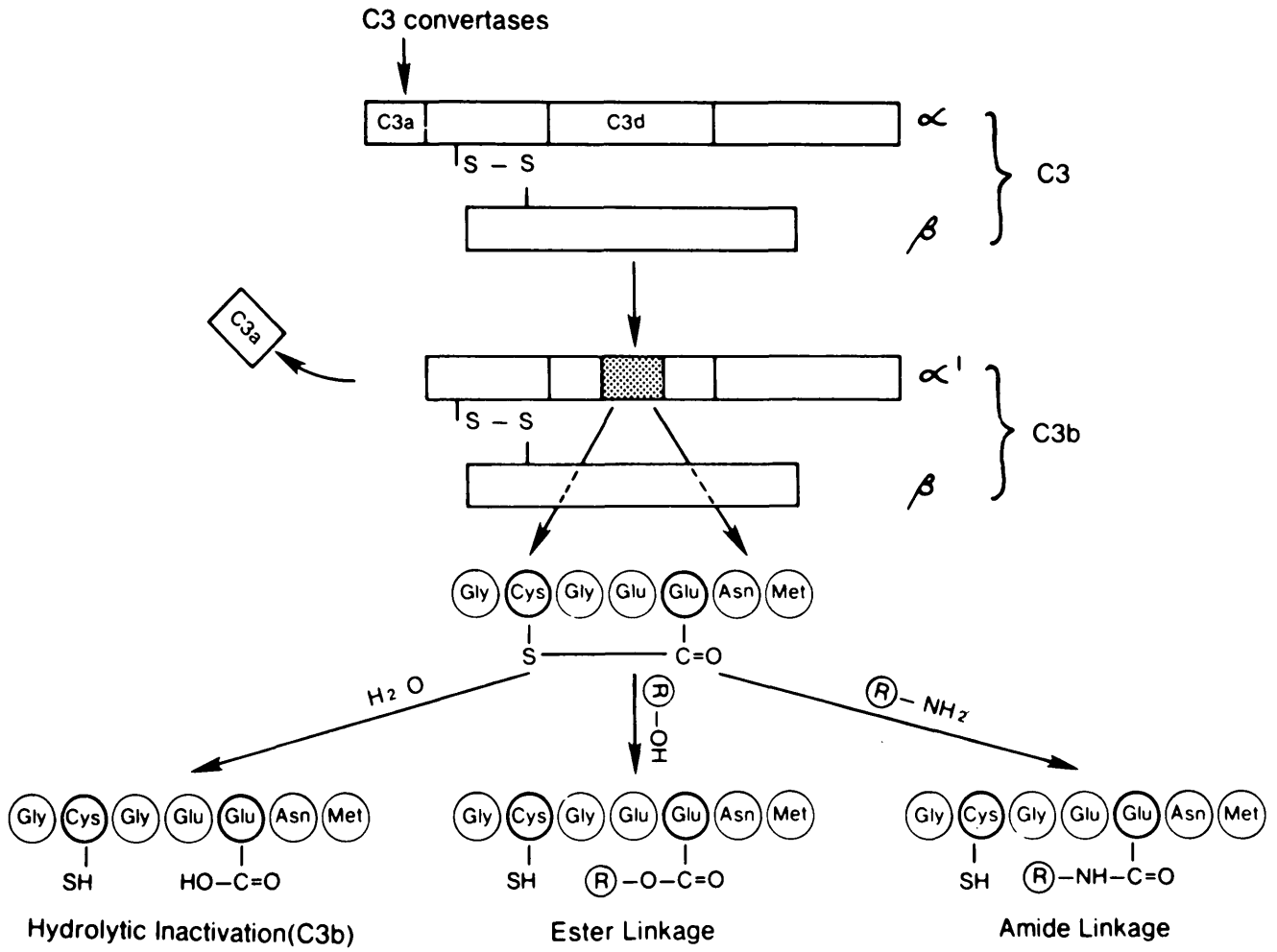

FIG. 1. Schematic diagram illustrating internal thiolester bond of C3 and 3 biochemical reactions at this site. In circulating C3, internal thiolester bond (*bold circles*) resides in C3d subdomain (*shaded area*). After enzymatic cleavage of C3a, exposure of thiolester bond facilitates covalent attachment of C3b to hydroxyl or amino groups on microbial surfaces. S-S, disulfide bond. (Reprinted from Gordon and Hostetter [26]).

cytosis, we defined an inhibitory role for hyperglycemia that is separate and distinct from its effects on the neutrophil. High concentrations of free glucose impair the opsonic function of C3 by binding to its thiolester site, a finding that provides a mechanism for the opsonic defect of hyperglycemia.

Several interesting possibilities arise from these experiments. First, in contrast to the passive glycosylation of serum proteins such as hemoglobin or albumin, the binding of glucose to C3 under conditions permitting complement activation significantly impairs its opsonic function. Second, a macrophage receptor for glycosylated proteins has recently been described and distinguished from other scavenger receptors on the basis of its interactions with modified ligands such as bovine serum albumin or low-density lipoproteins or with inhibiting polyanions (32). Although the original description of this receptor explored its specificity for advanced-glycosylation end products, which are formed in vitro after 4–6 wk of incubation with 50 mM glucose, the possibility that glycosylated C3 may interact with such receptors is intriguing. The binding of glycosylated C3 to macrophages may elicit inflammatory mediators such as cachectin or other interleukins, which may enhance tissue damage. These possibilities can now be tested with unmodified and glycosylated C3 ligands in in vitro systems. The potential for glucose-induced dysfunction of other opsonins, such as immunoglobulin molecules, deserves further investigation.

ENHANCEMENT OF CANDIDAL VIRULENCE BY HYPERGLYCEMIA

In addition to the impairment of humoral host defenses, some organisms appear particularly well equipped for survival in the hyperglycemic environment. For example, synthesis of an insulinlike hormone has been detected in *E. coli*, an organism commonly involved in infections of the gall bladder, urinary tract, or soft tissues in the hyperglycemic patient (33,34). *Pseudomonas testosteroni* has evolved a primitive system of cytosolic steroid receptors (35); whether *P. aeruginosa*, frequently implicated in invasive infections in diabetic hosts, possesses similar receptors is unknown. Such proteins may potentiate the virulence of the organism in the presence of exogenous steroids.

Like *Pseudomonas*, the eukaryote *C. albicans* also possesses cytosolic receptors for mammalian steroids, including corticosterone and progesterone, and synthesizes a

lipid-extractable moiety that competes with corticosterone for mammalian glucocorticoid receptors (36). Although no physiological function has yet been demonstrated, it is intriguing to speculate that exogenous steroids may directly mediate candidal virulence.

Recent studies have indicated that the yeast *C. albicans* possesses other unique features that promote its virulence in the hyperglycemic environment. Studies with complement-coated sheep erythrocytes (37,38) and with various monoclonal antibodies (38,39) have shown that this yeast expresses a surface protein that is antigenically akin to α-chain epitopes of the complement receptor CD11b/CD18, a protein found on mammalian phagocytes. As shown in studies from our laboratory, expression of the yeast protein is increased four- to sixfold when the concentration of glucose in the growth medium is raised from 5 to 50 mM, although rate of growth does not differ (39,40). Indeed, in a recent survey of >20 patient isolates of *C. albicans* from the University of Minnesota Hospital, all strains expressed this receptor to varying degree. More important, hyperglycemia, with a plasma glucose ≥200 mg/dl within 3 days before the isolation of *C. albicans*, was found to be the most common risk factor for candida infection and occurred in ~60% of patients, whereas neutropenia was present in <10% (40).

The utilization of glucose by *C. albicans* has important physiological consequences, both for the host and for the organism. First, expression of the yeast protein increases in dose-dependent fashion as the concentration of glucose in the medium increases from 1 to 20 mM. Although receptor expression is negligible at glucose concentrations between 1 and 10 mM, an abrupt increase in expression of the yeast protein is seen when the glucose concentration increases from 10 to 20 mM. These results imply that virulence factors in the yeast respond definitively to environmental glucose. Growth of the yeast in equimolar carbon sources such as 20 mM L-glutamate fails to increase expression of the yeast protein, as does growth in 2-deoxy-D-glucose, a nonmetabolizable sugar. Identification of the candidal protein by immunoprecipitation (41) or by Western blotting and immunodetection (40) has confirmed a single-chain structure of 145,000 ± 15,000 M_r, which approximates the molecular weight of the α-chain of the neutrophil complement receptor (CD11b); the protein is present in membrane and cytosolic extracts of the yeast (40). Such intracellular pools may serve as central reservoirs for this protein, which then responds to increased environmental glucose by translocation to the yeast membrane.

Two functions for the yeast protein have been confirmed. Work from our laboratory has demonstrated that the presence of this protein on *C. albicans* in yeast or mycelial phase impairs phagocytic recognition by virtue of its ability to bind the C3 ligand iC3b noncovalently (Fig. 2; 39). In these studies, blockade of the candidal protein with IgM monoclonal antibodies directed against its counterpart on the human neutrophil restored normal phagocytosis. Phagocytosis is also impaired when yeasts are grown in 20 mM glucose, compared with 20 mM D-glutamate, even though neutrophils are not exposed to the hyperglycemic environment (40). Glucose-induced virulence of *C. albicans* rather than neutrophil derangement may explain the impairment of phagocytic killing noted with similar concentrations of glucose (42).

More recent studies have expanded the functions of the candidal protein by characterizing its abilities to mediate adhesion of the yeast to endothelial surfaces; again, preincubation of the yeast with monoclonal antibodies recognizing the neutrophil homologue blocked candidal adhesion (43). The fascinating homology between the yeast protein and its mammalian counterpart CD11b/CD18, which is known to mediate neutrophil adhesion, suggests a role for the yeast protein in adhesion of *C. albicans* to other host tissues such as vaginal or buccal epithelium or even to foreign polymers such as Silastic. Increased expression of this protein in a hyperglycemic environment may therefore con-

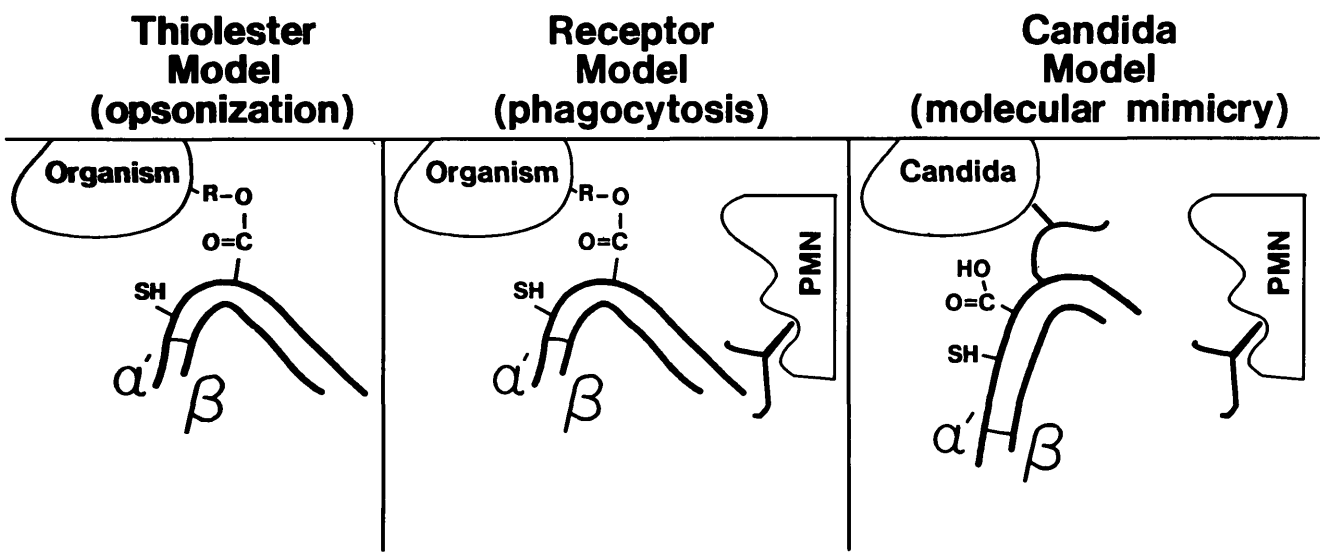

FIG. 2. Model of opsonic binding (*left*), which is mediated by covalent attachment of C3b to hydroxyl or amino groups on bacterial surface via C3-thiolester bond. PMN, polymorphonuclear leukocyte. Phagocytic receptors for C3 ligands (*center*) recognize conformation of covalently bound C3b or its degradation fragments and attach noncovalently, thereby initiating ingestion and killing. Presence of receptorlike protein on *Candida albicans* (*right*) subverts this system by binding iC3b noncovalently, so that complement-mediated phagocytosis is inhibited. (Reprinted from Gilmore et al. [39]. © by The University of Chicago Press.)

tribute directly to the increased pathogenicity of *C. albicans* in hyperglycemic hosts and in those patients with intravascular foreign bodies such as Silastic catheters. Cloning of complementary DNA for the candidal protein should provide definitive evidence regarding its relationship to mammalian adhesins and to the larger family of integrins from which they derive.

Studies such as these support the hypothesis that hyperglycemia alone is sufficient for significant impairment of humoral host defenses. Attachment of glucose to the opsonic binding site within the C3 thiolester can divert this important protein from the surface of invading bacteria and generate instead a dysfunctional C3-glucose complex, which is opsonically impotent. It remains to be seen whether glycosylated C3 can interact with macrophage receptors recognizing glucose-modified proteins or whether glycosylation of other opsonins, such as immunoglobulins, results in a similar impairment of function. Compounding these effects is the augmented virulence that accrues by several novel mechanisms when pathogens such as *E. coli*, *Pseudomonas* species, or *C. albicans* replicate in the hyperglycemic environment. Under these circumstances, impairment of neutrophil function and opsonic efficacy serves to promote the virulence of pathogens uniquely equipped to profit by the hyperglycemic environment.

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