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BIOLOGICAL ACTIVITIES OF C1 INHIBITOR

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Abstract

Broadly speaking, C1 inhibitor plays important roles in the regulation of vascular permeability and in the suppression of inflammation. Vascular permeability control is exerted largely through inhibition of two of the proteases involved in the generation of bradykinin, factor XIIa and plasma kallikrein (the plasma kallikrein-kinin system). Anti-inflammatory functions, however, are exerted via several activities including inhibition of complement system proteases (C1r, C1s, MASP2) and the plasma kallikrein-kinin system proteases, in addition to interactions with a number of different proteins, cells and infectious agents. These more recently described, as yet incompletely characterized, activities serve several potential functions, including concentration of C1 inhibitor at sites of inflammation, inhibition of alternative complement pathway activation, inhibition of the biologic activities of gram negative endotoxin, enhancement of bacterial phagocytosis and killing, and suppression of the influx of leukocytes into a site of inflammation. C1 inhibitor has been shown to be therapeutically useful in a variety of animal models of inflammatory diseases, including gram negative bacterial sepsis and endotoxin shock, suppression of hyperacute transplant rejection, and treatment of a variety of ischemia-reperfusion injuries (heart, intestine, skeletal muscle, liver, brain). In humans, early data appear particularly promising in myocardial reperfusion injury. The mechanism (or mechanisms) of the effect of C1 inhibitor in these conditions is (are) not completely clear, but involve inhibition of complement and contact system activation, in addition to variable contributions from other C1 inhibitor activities that do not involve protease inhibition.

Keywords

complement system; plasma kallikrein-kinin system; serpins; gram negative sepsis; ischemia-reperfusion injury; hyperacute transplant rejection; leukocyte rolling

1. Introduction

The biologic activities of C1 inhibitor may be divided into two broad categories: the regulation of vascular permeability and anti-inflammatory functions. Although vascular permeability and its control clearly are important in inflammatory processes, it is considered as a distinct separate activity because of its role in maintaining endothelial integrity. This importance is most dramatically demonstrated in hereditary angioedema, the disease that results from deficiency of C1 inhibitor protease inhibitor function. This role in the maintenance of vascular integrity is a result of C1 inhibitor-mediated regulation of contact system activation which results in

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modulation of the generation of bradykinin. The anti-inflammatory effects of C1 inhibitor appear to result from a variety of activities. These include, most obviously, the regulation of both complement and contact system activation, but also appear to include several activities that are not dependent on protease inhibition. This review will focus on these anti-inflammatory effects of C1 inhibitor. We will first discuss the different specific activities of C1 inhibitor that have been described, and will then summarize the results of studies that have evaluated the effects of treatment with C1 inhibitor in a number of inflammatory disease states.

1.1 Biochemistry of C1 inhibitor

C1 inhibitor is a member of the serpin family of protease inhibitors. Its structure and mechanism of protease inactivation are similar to other members of the family. Protease inactivation by serpins depends on a trapping mechanism that is activated following recognition, by protease, of the reactive center loop, which is displayed above the surface of the molecule. Cleavage of the peptide bond (P1-P1') at the reactive center triggers a molecular rearrangement and results in covalent bond formation between the P1 residue of the inhibitor and the active site serine of the protease. C1 inhibitor inactivates a variety of proteases including complement system proteases (C1r, C1s, MASP2), contact system proteases (factor XII, plasma kallikrein), an intrinsic coagulation protease (factor XI) and the fibrinolytic proteases (plasmin, tissue plasminogen activator). C1 inhibitor differs from other members of the serpin family in that it contains a long amino terminal domain of approximately 100 amino acid residues that is heavily glycosylated with both N- and O-linked sugars (Bock et al., 1986). The recently reported crystal structure of a latent form of the serpin domain of C1 inhibitor pointed out several unique features of the C1 inhibitor molecule, in addition to its similarities to other serpins (Beinrohr et al., 2007). The structural data also lent insight into the functional consequences of some naturally occurring mutant C1 inhibitors and has likely identified the heparin binding region on the surface of the molecule.

2. Activities of C1 Inhibitor

The most important activity of C1 inhibitor is protease inhibition. However, in addition to this function, a number of studies have described the non-covalent interaction of C1 inhibitor with a variety of other substances. These include extracellular matrix components, the complement component C3, endothelial cells and leukocytes, gram negative endotoxin and several infectious agents. These interactions do not appear to depend upon protease inhibitor function, but are believed, at least in some cases, to have potentially important functional consequences.

2.1 Protease inhibition

C1 inhibitor was discovered in 1957 by Ratnoff and Lepow, who described a heat labile factor in human plasma that inhibited the esterolytic activity of the first component of complement (Ratnoff and Lepow, 1957). Later studies demonstrated that C1 inhibitor inactivates both C1r and C1s, and that it is the only plasma protease inhibitor that regulates classical complement pathway activation (Sim et al., 1979b; Ziccardi, 1981). During complex formation, C1 inhibitor dissociates C1r and C1s from the activated C1 macromolecule, a process that is determined primarily by the interaction with C1r (Laurell et al., 1976; Sim et al., 1979a; Ziccardi and Cooper, 1979). It may also suppress spontaneous activation of C1 via a reversible interaction with zymogen C1r and C1s (Folkerd et al., 1980; Ziccardi, 1985). C1 inhibitor also regulates lectin pathway activation via inactivation of MASP2, although α_2 macroglobulin also is able to inhibit MASP2 (Kerr et al., 2008; Matsushita et al., 2000; Petersen et al., 2000).

The contact system, or the plasma kallikrein-kinin system, was originally described as a group of proteins in plasma that are activated following the addition of exogenous negatively charged substances. The major components are factor XII, plasma prekallikrein, factor XI and high

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molecular weight kininogen. Activation eventuated in the generation of bradykinin and in activation of the intrinsic coagulation pathway. It has subsequently become clear that a variety of biologic activities may eventuate following activation of the system and that, *in vivo*, there may be more than one mechanism of activation (Gailani and Renne, 2007; Sainz et al., 2007; Schmaier, 2007). C1 inhibitor, via inactivation of activated plasma kallikrein, factor XIIa and factor XIa, is the primary regulator of the plasma kallikrein-kinin system. The first evidence for this, although not appreciated at the time, was the observation of Landerman *et al* that plasma from patients with hereditary angioedema was deficient in kallikrein inhibitory capacity (Landerman et al., 1962). Subsequently, a number of studies demonstrated that, although α_2 macroglobulin also is able to inhibit both plasma kallikrein and factor XIIa, C1 inhibitor is responsible for the majority of the inhibition of these proteases (Gigli et al., 1970; Harpel et al., 1985; McConnell, 1972; Schapira et al., 1982; van der Graaf et al., 1983). As an example, the rate of kallikrein inactivation in C1 inhibitor deficient plasma is dramatically slower in comparison with normal plasma, while in α_2 macroglobulin deficient plasma the rate is only slightly slower (van der Graaf et al., 1983).

C1 inhibitor also can inactivate several other proteases, including plasmin and tissue plasminogen activator (tPA)(Harpel and Cooper, 1975; Huisman et al., 1995; Ranby et al., 1982; Ratnoff et al., 1969; Sulikowski and Patston, 2001). Although C1 inhibitor does not appear to play a significant role in the inactivation of plasmin *in vivo*, it may, under some circumstances, contribute to inactivation of tPA (Aoki et al., 1977; Harpel, 1981; Huisman et al., 1995). In addition, thrombin is generated during attacks of hereditary angioedema and C1 inhibitor, *in vitro*, can form complexes with thrombin (Cugno et al., 2001; Cugno et al., 1997). However, the slow rate of complex formation and the lack of a demonstrable interaction in plasma suggests that inhibition in circulating blood is probably not important, but enhanced complex formation in the presence of heparin suggested that it could be important at endothelial surfaces (Cugno et al., 2001).

2.2 Interaction with extracellular matrix and other endogenous proteins

C1 inhibitor, via a reversible interaction with C3b that appears to interfere with the C3b-factor B interaction, also can inhibit alternative pathway activation (Jiang et al., 2001). This interaction does not require protease inhibition. This mechanism appears similar to that of factor H interference with formation of the alternative pathway convertase. Although inhibition of alternative pathway activation was apparent at physiologic concentrations, its *in vivo* biologic importance has not yet been determined. Using ligand blotting assays and ELISA, Patston and Schapira demonstrated that C1 inhibitor binds to the extracellular matrix proteins type IV collagen, laminin, and entactin (Patston and Schapira, 1997). Half-maximal binding to both collagen and laminin occurred at a C1 inhibitor concentration of approximately 8 μg/ml. Cleavage of C1 inhibitor at Pro^{36} with *Crotalus atrox* α-proteinase did not interfere with binding. Binding had no effect on inhibitory function by C1 inhibitor, as measured by determination of the rate constant for inhibition of C1s. The biochemical nature of the binding of C1 inhibitor to collagen, laminin and entactin has not been further characterized. Tissue transglutaminase, but not factor XIII, is able to cross-link C1 inhibitor, via Gln^{453} to immobilized fibrin (Hauert et al., 2000). This cross-linked C1 inhibitor retains protease inhibitory activity. The biologic relevance of these reactions has not been defined. However, it seems possible, at the least, that these reactions with extracellular matrix proteins may result in concentration of C1 inhibitor at extra-vascular sites of inflammation in order to enhance regulation of local complement and contact system activation.

2.3 Interactions of C1 inhibitor with cells

C1 inhibitor has been reported to bind to human neutrophils in a reaction that did not depend on protease inhibitor activity and that appeared to be mediated via the heavily glycosylated

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amino terminal domain (Chang et al., 1991). A possible biologic role for this interaction has not been determined. More recently, we have demonstrated that C1 inhibitor appears to enhance phagocytosis and/or killing by neutrophils and macrophages of bacteria from mice with peritonitis and sepsis secondary to cecal ligation and puncture (Liu et al., 2007). The mechanism responsible for this increase in bacterial killing has not been determined.

C1 inhibitor binds to cultured endothelial cells in a concentration dependent manner and this binding is enhanced two- to three-fold by prolonged incubation at 4°C (Bergamaschini et al., 2001). Bound C1 inhibitor retained the ability to inhibit C1s. Furthermore, C1 inhibitor was shown to bind to liver sinusoidal endothelial cells during hypothermic storage and the addition of C1 inhibitor during *in vitro* reperfusion suppressed complement activation and protected the liver from ischemia-reperfusion-induced damage.

C1 inhibitor expresses the sialyl Lewis^x tetrasaccharide on one or more of its six N-linked carbohydrates (Cai and Davis III, 2003). Most E-, P- and L-selectin ligands contain a peripheral fucose that is attached by an α1,3-glycosidic linkage to the sialyl Lewis^x tetrasaccharide. C1 inhibitor was shown to bind to E- and P-selectins, both on cell surfaces and in the fluid phase. The presence of C1 inhibitor in culture medium at concentrations in the same range as those achieved in blood during inflammatory responses suppressed the adhesion of macrophages to cultured endothelial cells. This effect is very likely mediated by competition for binding to selectins expressed on the endothelial cell surface. These results are consistent with, and may explain the mechanism, for the binding of C1 inhibitor to endothelial cells described above (Bergamaschini et al., 2001). Also consistent with all these findings is the observation that E-selectin expression on endothelial cells is up-regulated following cold perfusion (Takada et al., 1997).

Additional studies demonstrated that C1 inhibitor and reactive center cleaved inactive C1 inhibitor (iC1 inhibitor), in a dose-dependent manner, inhibited the binding of another E-selectin ligand, carcinoembryonic antigen, to recombinant E-selectin expressed on CHO cells (Cai et al., 2005). Furthermore, C1 inhibitor (and iC1 inhibitor) inhibited the rolling of leukocytes *in vitro* on both immobilized E-selectin and on P-selectin transfected cells. Finally, both forms of C1 inhibitor interfered significantly with TNF-α induced leukocyte rolling in mice (Cai et al., 2005). However, both *in vitro* and *in vivo*, N-deglycosylated C1 inhibitor lost the ability to interfere with leukocyte rolling which is consistent with the hypothesis that this activity is mediated by interference with the interaction with E- and/or P-selectin.

2.4 Interactions of C1 inhibitor with infectious agents

StcE, a metalloprotease secreted by *E. coli* O157:H7 cleaves C1 inhibitor at a site that appears to be within the amino terminal heavily glycosylated domain (Lathem et al., 2002). In hemolytic assays, this cleaved C1 inhibitor had increased inhibitory activity that appeared to result from acquisition of the ability of the cleaved C1 inhibitor to bind to the erythrocyte surface (Lathem et al., 2004). The data indicated that the C1 inhibitor very likely was bound to StcE, which itself bound to the erythrocyte surface. This led to concentration of C1 inhibitor at the cell surface resulting in enhanced inhibition of complement activation. Therefore, this mechanism may provide *E. coli* O157:H7 with the ability to evade complement-mediated killing and may even suppress complement activation at sites distant from the site of infection (Lathem et al., 2004).

Another potential mechanism to evade complement-mediated killing of bacteria has been described in which virulent strains of *Bordetella pertussis* were shown to bind C1 inhibitor (Marr et al., 2007). Binding correlated quite well with serum resistance. Neither the mechanism of binding nor the relative contribution of C1 inhibitor binding to serum resistance have been defined. Interestingly, unlike binding to gram negative endotoxin (see below), the binding of

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C1 inhibitor to *Bordetella* required an intact reactive center loop but was unaffected by deglycosylation.

C1 inhibitor has been shown to bind directly to gram negative endotoxin, specifically to *Salmonella typhimurium* LPS (Liu et al., 2003), although subsequently binding to other gram negative endotoxins and to intact gram negative organisms has been demonstrated (unpublished data). Binding is mediated via lipid A, which is the component of LPS primarily responsible for the pathophysiology of endotoxin shock. Binding to LPS is not dependent upon protease inhibitory function but is dependent upon the heavily glycosylated amino terminal non-serpin domain (Liu et al., 2004). Site directed mutagenesis studies indicate that binding is mediated via the four basic amino acids (Arg^{18}, Lys^{22}, Lys^{30}, Lys^{55}) within this domain; in addition, N-glycosylation at Asn^{3} appears to be necessary to maintain an appropriate binding conformation of the amino terminal domain (Liu et al., 2005a). Binding of C1 inhibitor prevents the interaction of LPS with the LPS receptor complex on the surface of macrophages, thereby suppressing the production of TNF-α (Liu et al., 2003). The data indicate that this mechanism plays a role in C1 inhibitor-mediated protection from endotoxin shock (Liu et al., 2003)(see Section 3.1).

In preliminary studies, C1 inhibitor has been shown by immunofluorescence analysis to bind to *Plasmodium falciparum* and to infected human red blood cells (Mejia, P., Davis, A. E., unpublished data). *Plasmodium falciparum* is the causative agent of the most serious form of human malaria (see section 3.3).

3. C1 inhibitor-mediated modulation of inflammatory disease

3.1 Sepsis and endotoxin shock

In many studies using different animal models over the past 15–20 years, administration of C1 inhibitor has been shown to result in improved survival and in correction of a number of different biochemical and physiologic parameters (Croner et al., 2004; Fischer et al., 1997; Giebler et al., 1999; Guerrero et al., 1993; Jansen et al., 1998; Lehmann et al., 2004; Liu et al., 2003; Scherer et al., 1996; Schmidt et al., 1999a; Schmidt et al., 1999b; Siebeck et al., 1987). Treatment with C1 inhibitor results in improvement in pulmonary dysfunction (Guerrero et al., 1993), a decrease in cytokine production (Jansen et al., 1998; Liu et al., 2003), evidence for decreased complement and contact system activation (Jansen et al., 1998), decreased leukocyte adherence and suppression of the increase in vascular permeability (Croner et al., 2004; Lehmann et al., 2004; Schmidt et al., 1999b). Some data indicate that the contact system may mediate some aspects of endotoxin shock, while other data suggest that it is not significantly involved (Colman, 1999; Feletou et al., 1996; Jansen et al., 1996; Pixley et al., 1993). The complement system very likely plays a dual role. C5a appears to be involved in the mediation of endotoxin shock (Barton and Warren, 1993; Czermak et al., 1999; Strachan et al., 2000). C3 and C4 deficient mice, however, are more susceptible than normal mice to endotoxin shock, in support of the hypothesis that C3 is required for normal endotoxin clearance (Fischer et al., 1997). Survival of C3 deficient mice is improved by treatment with C1 inhibitor. Therefore, it is unlikely that the C1 inhibitor effect in septic shock is solely mediated via inhibition of complement activation.

Protection from endotoxin shock, in our studies, was provided both by intact, active C1 inhibitor and by reactive center cleaved C1 inhibitor, which retains no protease inhibitory activity (Liu et al., 2003). Treatment with both forms of C1 inhibitor resulted in prolonged survival, decreased production of TNF-α, and suppression of increased vascular permeability changes in response to endotoxin (Liu et al., 2003; Liu et al., 2005b). As described above, these effects are at least partially, perhaps largely, mediated by the direct binding of C1 inhibitor to LPS, which prevents its interaction with macrophages and endothelial cells. Although

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inhibition of complement and contact system activation probably does play a role, the observation that inactive C1 inhibitor is effective suggests that, in this model, the direct interaction with endotoxin plays the dominant role.

The cecal ligation and puncture model of peritonitis and sepsis is a more clinically relevant model of sepsis than models induced either by injection of LPS or of intact gram negative bacteria (Deitch, 1997). In this model, treatment with C1 inhibitor (or inactive C1 inhibitor) improved survival in comparison with untreated controls (Liu et al., 2007). The enhanced survival was accompanied by diminished numbers of viable bacteria in the blood and peritoneal fluid, evidence for improved phagocyte function and decreased levels of TNF-α in comparison with untreated controls. *In vitro*, C1 inhibitor bound to the bacteria cultured from mice with cecal ligation and puncture, and improved the phagocytosis and/or killing of these bacteria by both neutrophils and macrophages (Liu et al., 2007). The mechanism responsible for this enhanced bacterial killing is under investigation.

Experience with the use of C1 inhibitor in human sepsis remains somewhat limited. In the early 1990's, it was reported that C1 inhibitor treatment of small numbers of patients with septic shock suppressed activation of both the complement (decreased C3a and C5a) and contact (increased factor XII and prekallikrein) systems (Hack et al., 1993; Hack et al., 1992). A single double blind, placebo-controlled trial has been reported (Caliezi et al., 2002). This study found that therapy with C1 inhibitor resulted in improved renal function and less severe multiple organ dysfunction. However, mortality rates were similar in the treated and untreated groups. This effect may be mediated via a reduction in neutrophil activation, perhaps via a suppression of IL-8 production (Zeerleder et al., 2003). Clearly, further studies analyzing the efficacy of C1 inhibitor in sepsis in humans is warranted.

3.2 Pneumococcal meningitis

In a rat model of meningitis with *Streptococcus pneumoniae*, treatment with C1 inhibitor improved clinical scores, improved bacterial clearance from the cerebrospinal fluid and blood, and decreased leukocyte infiltration into the meninges and cerebrospinal fluid (Zwijnenburg et al., 2007). The increased bacterial clearance may have been a result of an increase in expression of CR3. Similar findings were observed in a mouse meningitis model (Zwijnenburg et al., 2007). In addition, inflammatory cytokines, except TNF-α, were up-regulated less in the treated than in the untreated mice. The mechanism (or mechanisms) for these effects remain (s) incompletely defined.

3.3 Malaria

In addition to binding to *Plasmodium falciparum* (section 2.4), C1 inhibitor has been shown in preliminary studies to decrease the ability of the parasite to infect human erythrocytes and to suppress the adhesion of infected erythrocytes to C32 human amelanotic melanoma monolayers (unpublished data). Furthermore, C1 inhibitor treatment provided protection *in vivo* using a mouse model of severe malaria. The mechanism of these effects and their potential relevance to human disease are being investigated.

3.4 Transplantation

Hyperacute transplant rejection is largely a result of natural antibody-mediated complement activation. This is particularly problematic in the case of xenotransplantation, which has been investigated rather extensively over the last 10–15 years. Inhibition of such complement activation with C1 inhibitor has been used in a number of *in vitro*, *ex vivo* and *in vivo* xenotransplantation models. Soluble C1 inhibitor inhibited the activation of porcine aortic endothelial cells incubated with human serum (Dalmasso and Platt, 1993). Surface bound C1 inhibitor also was shown to protect Chinese hamster ovary cells and pig endothelial cells from

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lysis by human complement (Fukuta et al., 2003; Matsunami et al., 2000). *Ex vivo* perfusion of pig kidneys with human blood plus additional C1 inhibitor prolonged survival by greater than four fold (Fiane et al., 1999). Complement, platelet and neutrophil activation were reduced in the treated compared with the control kidneys. Similar results were obtained using *ex vivo* pig lung- or mouse lung-whole human blood models, although injury was not completely prevented (Schelzig et al., 2001; Schroder et al., 2003). In another study, the addition of C1 inhibitor did not further prolong the survival of *ex vivo* human blood perfused human CD55 transgenic pig lungs (Poling et al., 2006). *In vivo*, soluble C1 inhibitor suppressed hyperacute rejection and acute vascular rejection of kidneys in pig to cynomolgus monkey models (Hecker et al., 2002; Przemek et al., 2002; Vangerow et al., 2001). On the other hand, transplantation of pig hearts transgenic for either human DAF or MCP into baboons treated with C1 inhibitor resulted in efficient complement inhibition (Wu et al., 2007). However, hyperacute rejection was not prevented. There is little information on the use of C1 inhibitor in transplantation in humans. One report described improvement in capillary leak syndrome in two lung transplant patients following treatment with C1 inhibitor (Struber et al., 1999). In conclusion, although a great deal of data in models is promising, it remains unclear whether C1 inhibitor may be a useful addition to treatment of either hyperacute transplant rejection or acute vascular rejection.

3.5 Ischemia-reperfusion injury

C1 inhibitor has been used extensively in animal models of ischemia-reperfusion injury. The largest amount of experience has been with myocardial reperfusion injury, in which several studies have shown that administration of C1 inhibitor at, or just before, reperfusion results in reduced myocardial injury, decreased numbers of neutrophils in the myocardium, reduction of plasma levels of creatine kinase, troponin T, C3a and C5a, and suppression of endothelial expression of P-selectin and ICAM-1 (Buerke et al., 1995; Buerke et al., 1998; Horstick et al., 2001; Horstick et al., 1997). Two recent studies have suggested an effect of C1 inhibitor on myocardial C3 expression and a direct suppression of ischemia-reperfusion induced apoptosis (Fu et al., 2006a; Fu et al., 2006b).

C1 inhibitor was used to treat three patients following emergency surgical revascularization after failed percutaneous transluminal coronary angioplasty and appeared to be associated with improved hemodynamic stability (Bauernschmitt et al., 1998). In 24 patients with myocardial infarction, C1 inhibitor therapy instituted following thrombolytic therapy resulted in diminished complement activation and reduction of troponin T and creatine kinase (de Zwaan et al., 2002). Another study compared C1 inhibitor treatment with a control group among patients with acute ST-elevation myocardial infarction who underwent emergency coronary artery bypass surgery (Thielmann et al., 2006). In agreement with the above study, the C1 inhibitor treated patients revealed reduced cardiac troponin I levels. More recently, a controlled randomised double-blind study of 80 similar patients also revealed reduced cardiac troponin I levels in the treated group, as well as significant improvement in mean arterial pressure, cardiac index, stroke volume and a variety of other clinical criteria (Fattouch et al., 2007). Clearly, further clinical analysis of the effect of C1 inhibitor in myocardial ischemia-reperfusion injury in humans is justified and needs to be encouraged.

Beneficial effects of C1 inhibitor also have been described in other ischemia-reperfusion injury models including skeletal muscle (Nielsen et al., 2002; Toomayan et al., 2003), liver (Heijnen et al., 2006; Inderbitzin et al., 2004; Lehmann et al., 2000), middle cerebral artery occlusion (Akita et al., 2003; De Simoni et al., 2004; De Simoni et al., 2003; Storini et al., 2005), and superior mesenteric artery occlusion (Karpel-Massler et al., 2003; Lauterbach et al., 2007; Padilla et al., 2007). Interestingly, the effect of C1 inhibitor in brain ischemia-reperfusion is apparently not mediated via inhibition of C1r/C1s because C1q deficient mice were susceptible to injury and responded to treatment with C1 inhibitor (De Simoni et al., 2004). It has not been

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determined whether this effect is mediated via inhibition of the lectin pathway, inhibition of the contact system or via some other mechanism. In this model, treatment with C1 inhibitor results in suppression of leukocyte infiltration, and of expression of P-selectin, ICAM-1, pro-inflammatory cytokines (TNF-α, IL-18) and pro-caspase 3, resulting in both an anti-inflammatory and anti-apoptotic effect (De Simoni et al., 2004; Storini et al., 2005). Reperfusion injury also plays a role in solid organ transplantation. C1 inhibitor has been used in dogs and sheep in lung transplant models and was shown to improve early pulmonary dysfunction (Graeter et al., 1997; Salvatierra et al., 1997). In hepatic ischemia-reperfusion injury, a marked reduction in the adherence of leukocytes to sinusoidal and venular endothelium also was noted (Lehmann et al., 2000). Similarly, C1 inhibitor treatment of mice subjected to intestinal-ischemia reperfusion injury suppresses complement activation, suppresses leukocyte adhesion and infiltration, and improves survival rates (Karpel-Massler et al., 2003; Lauterbach et al., 2007; Padilla et al., 2007).

We have recently analyzed the mechanism of C1 inhibitor-mediated alleviation of intestinal ischemia-reperfusion injury (Lu, F. and Davis, A. E., unpublished data). C1 inhibitor suppressed injury in wild type, bradykinin 2 receptor deficient and C3 deficient mice. This histologic improvement was associated with decreased neutrophil infiltration (as reflected by reduced intestinal myeloperoxidase levels), decreased serum LDH levels, and decreased TNF-α levels. In wild type mice, treatment with reactive center cleaved inactive C1 inhibitor had the same effects and, as with active C1 inhibitor, improved survival rates. Furthermore, both active and inactive C1 inhibitor suppressed leukocyte rolling in the mesenteric vasculature of both wild type and C3 deficient mice subjected to intestinal ischemia-reperfusion injury. Therefore, at least in this model, it appears that the anti-inflammatory effect of C1 inhibitor is mediated both by inhibition of complement and contact system proteases, and by other mechanisms. Based on previous data (discussed in Section 2.3), we have hypothesized that C1 inhibitor suppresses leukocyte rolling and infiltration, at least partly by virtue of its ability to interact with E- and P-selectins on the endothelial surface.

4. Concluding remarks

C1 inhibitor has proven to be effective in a surprising number of models of inflammatory disease. In most of these models, at least some portion of the damage is mediated via complement system activation. The effectiveness of C1 inhibitor has, therefore, largely been assumed to result from inhibition of complement activation. Such inhibition is almost certainly the explanation for a portion of the improvement observed with C1 inhibitor treatment in these animal models. However, inhibition of the plasma kallikrein-kinin system proteases, as well as C1 inhibitor-mediated activities that do not depend on protease inhibition appear to be involved in suppression of inflammation. In particular, a direct effect of C1 inhibitor on inhibition of the activity of gram negative bacterial endotoxin, enhancement of phagocytosis, and suppression of leukocyte rolling and transmigration across the endothelium to sites of inflammation may play a role.

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References

Akita N, Nakase H, Kaido T, Kanemoto Y, Sakaki T. Protective effect of C1 esterase inhibitor on reperfusion injury in the rat middle cerebral artery occlusion model. Neurosurgery 2003;52:395–400. [PubMed: 12535370]

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Aoki N, Moroi M, Matsuda M, Tachiya K. The behavior of alpha2-plasmin inhibitor in fibrinolytic states. J Clin Invest 1977;60:361–369. [PubMed: 68962]

Barton PA, Warren JS. Complement component C5 modulates the systemic tumor necrosis factor response in murine endotoxic shock. Infect Immun 1993;61:1474–1481. [PubMed: 8454352]

Bauernschmitt R, Bohrer H, Hagl S. Rescue therapy with C1-esterase inhibitor concentrate after emergency coronary surgery for failed PTCA. Intensive Care Med 1998;24:635–638. [PubMed: 9681790]

Beinrohr L, Harmat V, Dobo J, Zsolt L, Gal P, Zavodszky P. C1 inhibitor serpin domain structure reveals the likely mechanism of heparin potentiation and conformational disease. J Biol Chem 2007;282:21100–21209. [PubMed: 17488724]

Bergamaschini L, Gobbo G, Gatti S, Caccamo L, Prato P, Maggioni M, Braidotti P, Di Stefano R, Fassati LR. Endothelial targeting with C1-inhibitor reduces complement activation in vitro and during ex vivo reperfusion of pig liver. Clin Exp Immunol 2001;126:412–420. [PubMed: 11737055]

Bock SC, Skriver K, Nielsen E, Thogersen HC, Wiman B, Donaldson VH, Eddy RL, Marrinan J, Radziejewska E, Huber R, Shows TB, Magnussen S. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. Biochemistry 1986;25:4292–4301. [PubMed: 3756141]

Buerke M, Murohara T, Lefer AM. Cardioprotective effects of a C1 esterase inhibitor in myocardial ischemia and reperfusion. Circulation 1995;91:393–402. [PubMed: 7805243]

Buerke M, Prufer D, Dahm M, Oelert H, Meyer J, Darius H. Blocking of classical complement pathway inhibits endothelial adhesion molecule expression and preserves ischemic myocardium from reperfusion injury. J Pharmacol Exp Ther 1998;286:429–438. [PubMed: 9655888]

Cai S, Davis AE III. Complement regulatory protein C1 inhibitor binds to selectins and interferes with endothelial-leukocyte adhesion. J Immunol 2003;171:4786–4791. [PubMed: 14568956]

Cai S, Dole V, Bergmeier W, Scafidi J, Feng H, Wagner DD, Davis AE III. A direct role for C1 inhibitor in leukocyte adhesion. J Immunol 2005;174:6462–6466. [PubMed: 15879149]

Caliezi C, Zeerleder S, Redondo M, Regli B, Rothen HU, Zurcher-Zenklusen R, Rieben R, Devay J, Hack CE, Lammle B, Wuilemin WA. C1-inhibitor in patients with severe sepsis and septic shock: beneficial effect on renal dysfunction. Crit Care Med 2002;30:1722–1728. [PubMed: 12163783]

Chang N-S, Boackle RJ, Leu RW. Characterization of C1 inhibitor binding to neutrophils. Immunology 1991;73:95–101. [PubMed: 2045131]

Colman RW. Biologic activities of the contact factors in vivo. Potentiation of hypotension, inflammation, and fibrinolysis, and inhibition of cell adhesion, angiogenesis and thrombosis. Thromb Haemost 1999;82:1568–1577. [PubMed: 10613636]

Croner RS, Lehmann TG, Fallsehr C, Herfarth C, Klar E, Kirschfink M. C1-inhibitor reduces hepatic leukocyte-endothelial interaction and the expression of VCAM-1 in LPS-induced sepsis in the rat. Microvasc Res 2004;67:182–191. [PubMed: 15020209]

Cugno M, Bos I, Lubbers Y, Hack CE, Agostoni A. In vitro interaction of C1-inhibitor with thrombin. Blood Coagul Fibrinolysis 2001;12:253–260. [PubMed: 11460008]

Cugno M, Cicardi M, Bottasso B, Coppola R, Paonessa R, Mannucci PM, Agostoni A. Activation of the coagulation cascade in C1-inhibitor deficiencies. Blood 1997;89:3213–3218. [PubMed: 9129025]

Czermak BJ, Sarma V, Pierson CL, Warner RL, Huber-Lang M, Bless NM, Schmal H, Priedl HP, Ward PA. Protective effects of C5a blockage in sepsis. Nature Medicine 1999;5:788–792.

Dalmasso AP, Platt JL. Prevention of complement-mediated activation of xenogeneic endothelial cells in an in vitro model of xenograft hyperacute rejection by C1 inhibitor. Transplantation 1993;56:1171–1176. [PubMed: 8249120]

De Simoni MG, Rossi E, Storini C, Pizzimenti S, Echart C, Bergamaschini L. The powerful neuroprotective action of C1-inhibitor on brain ischemia-reperfusion injury does not require C1q. Am J Pathol 2004;164:1857–1863. [PubMed: 15111332]

De Simoni MG, Storini C, Barba M, Catapano L, Arabia AM, Rossi E, Bergamaschini L. Neuroprotection by complement (C1) inhibitor in mouse transient brain ischemia. J Cereb Blood Flow Metab 2003;23:232–239. [PubMed: 12571454]

de Zwaan C, Kleine AH, Diris JH, Glatz JF, Wellens HJ, Strengers PF, Tissings M, Hack CE, van Dieijen-Visser MP, Hermens WT. Continuous 48-h C1-inhibitor treatment, following reperfusion therapy, in patients with acute myocardial infarction. Eur Heart J 2002;23:1670–1677. [PubMed: 12398824]

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Deitch EA. Animal models of sepsis and shock: a review and lessons learned. Shock 1997;9:1–11. [PubMed: 9466467]

Fattouch K, Bianco G, Speziale G, Sampognaro R, Lavalle C, Guccione F, Dioguardi P, Ruvolo G. Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double-blind study. Eur J Cardiothorac Surg 2007;32:326–332. [PubMed: 17576071]

Feletou M, Jamonneau I, Germain M, Thurieau C, Fauchere JL, Villa P, Ghezzi P, Canet E. Bradykinin B2 receptor involvement in rabbit and murine models of septic shock. J Cardiovasc Pharmacol 1996;27:500–507. [PubMed: 8847866]

Fiane AE, Videm V, Johansen HT, Mellbye OJ, Nielsen EW, Mollnes TE. C1-inhibitor attenuates hyperacute rejection and inhibits complement, leukocyte and platelet activation in an ex vivo pig-to-human perfusion model. Immunopharmacology 1999;42:231–243. [PubMed: 10408384]

Fischer MB, Prodeus AP, Nicholson-Weller A, Ma M, Murrow J, Reid RR, Warren HB, Lage AL, Moore J, F D, Rosen FS, Carroll MC. Increased susceptibility to endotoxin shock in complement C3- and C4-deficient mice is corrected by C1 inhibitor replacement. J Immunol 1997;159:976–982. [PubMed: 9218619]

Folkerd EJ, Gardner B, Hughes-Jones NC. The relationsip between the binding ability and the rate of activation of the complement component C1. Immunol 1980;41:179–185.

Fu J, Lin G, Wu Z, Ceng B, Wu Y, Liang G, Qin G, Li J, Chiu I, Liu D. Anti-apoptotic role for C1 inhibitor in ischemia/reperfusion-induced myocardial cell injury. Biochem Biophys Res Commun 2006a; 349:504–512. [PubMed: 16942749]

Fu J, Lin G, Zeng B, Wu Z, Wu Y, Chu H, Qin G, Liang G, Li J, Gan X, Yu X, Li C, Liu D. Anti-ischemia/reperfusion of C1 inhibitor in myocardial cell injury via regulation of local myocardial C3 activity. Biochem Biophys Res Commun 2006b;350:162–168. [PubMed: 16996480]

Fukuta D, Miyagawa S, Yamada M, Matsunami K, Kurihara T, Shirasu A, Hattori H, Shirakura R. Effect of various forms of the C1 esterase inhibitor (C1-INH) and DAF on complement mediated xenogeneic cell lysis. Xenotransplantation 2003;10:132–141. [PubMed: 12588646]

Gailani D, Renne T. The intrinsic pathway of coagulation: a target for treating thromboembolic disease? J Thromb Haemost 2007;5:1106–1112. [PubMed: 17388803]

Giebler R, Schmidt U, Koch S, Peters J, Scherer R. Combined antithrombin III and C1-esterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to Escherichia coli endotoxin. Crit Care Med 1999;27:597–604. [PubMed: 10199542]

Gigli I, Mason JW, Colman RW, Austen KF. Interaction of plasma kallikrein with the C1 inhibitor. J Immunol 1970;104:574–581. [PubMed: 5435787]

Graeter T, Demertzis S, Scherer M, Langer F, Eisele B, Schafers HJ. Amelioration of ischemia/reperfusion injury with C1-esterase inhibitor in a sheep lung transplant model. Ann Haematol 1997;74:A156.

Guerrero R, Velasco F, Rodriguez M, Lopez A, Rojas R, Alvarez MA, Villalba R, Rubio V, Torres A, Castillo Dd. Endotoxin-induced pulmonary dysfunction is prevented by C1-esterase inhibitor. J Clin Invest 1993;91:2754–2760. [PubMed: 8514883]

Hack CE, Ogilvie AC, Eisele B, Eerenberg AJ, Wagstaff J, Thijs LG. C1-inhibitor substitution therapy in septic shock and in the vascular leak syndrome induced by high doses of interleukin-2. Intensive Care Med 1993;19:S19–S28. [PubMed: 8053997]

Hack CE, Voerman HJ, Eisele B, Keinecke HO, Nuijens JH, Eerenberg AJ, Ogilvie A, Strack van Schijndel RJ, Delvos U, Thijs LG. C1-esterase inhibitor substitution in sepsis. Lancet 1992;339:378. [PubMed: 1346464]

Harpel PC. Alpha2-plasmin inhibitor and alpha2-macroglobulin-plasmin complexes in plasma. Quantitation by an enzyme-linked differential antibody immunosorbent assay. J Clin Invest 1981;68:46–55. [PubMed: 6166634]

Harpel PC, Cooper NR. Studies on human plasma C1-inactivator-enzyme interactions. I. Mechanisms of interaction with C1s, plasmin and trypsin. J Clin Invest 1975;55:593–604. [PubMed: 123251]

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Harpel PC, Lewin MF, Kaplan AP. Distribution of plasma kallikrein between C1 inactivator and a2-macroglobulin in plasma utilizing a new assay for a2-macroglobulin-kallikrein complexes. J Biol Chem 1985;260:4257–4263. [PubMed: 2579948]

Hauert J, Patston PA, Schapira M. C1 inhibitor cross-linking by tissue transglutaminase. J Biol Chem 2000;275:14558–14562. [PubMed: 10799541]

Hecker JM, Lorenz R, Appiah R, Vangerow B, Loss M, Kunz R, Schmidtko J, Mengel M, Klempnauer J, Piepenbrock S, Dickneite G, Neidhardt H, Ruckoldt H, Winkler M. C1-inhibitor for prophylaxis of xenograft rejection after pig to cynomolgus monkey kidney transplantation. Transplantation 2002;73:675–677. [PubMed: 11907409]

Heijnen BH, Straatsburg IH, Padilla ND, Van Mierlo GJ, Hack CE, Van Gulik TM. Inhibition of classical complement activation attenuates liver ischaemia and reperfusion injury in a rat model. Clin Exp Immunol 2006;143:15–23. [PubMed: 16367929]

Horstick G, Berg O, Heimann A, Gotze O, Loos M, Hafner G, Bierbach B, Petersen S, Bhakdi S, Darius H, Horstick M, Meyer J, Kempski O. Application of C1-esterase inhibitor during reperfusion of ischemic myocardium: dose-related beneficial versus detrimental effects. Circulation 2001;104:3125–3131. [PubMed: 11748112]

Horstick G, Heimann A, Gotze O, Hafner G, Berg O, Bohmer P, Becker P, Darius H, Rupprecht HJ, Loos M, Bhakdi S, Meyer J, Kempski O. Intracoronary application of C1 esterase inhibitor improves cardiac function and reduces necrosis in an experimental model of ischemia reperfusion. Circulation 1997;95:701–708. [PubMed: 9024160]

Huisman LG, van Griensven JM, Kluft C. On the role of C1-inhibitor as inhibitor of tissue-type plasminogen activator in human plasma. Thromb Haemost 1995;73:466–471. [PubMed: 7667830]

Inderbitzin D, Beldi G, Avital I, Vinci G, Candinas D. Local and remote ischemia-reperfusion injury is mitigated in mice overexpressing human C1 inhibitor. Eur Surg Res 2004;36:142–147. [PubMed: 15178902]

Jansen PM, Eisele B, de Jong IW, Chang A, Delvos U, Taylor J, F B, Hack CE. Effect of C1 inhibitor on inflammatory and physiologic response patterns in primates suffering from lethal septic shock. J Immunol 1998;160:475–484. [PubMed: 9552006]

Jansen PM, Pixley RA, Brouwer M, de Jong IW, Chang AC, Hack CE, Taylor FB Jr, Colman RW. Inhibition of factor XII in septic baboons attenuates the activation of complement and fibrinolytic systems and reduces the release of interleukin-6 and neutrophil elastase. Blood 1996;87:2337–2344. [PubMed: 8630396]

Jiang H, Wagner E, Zhang H, Frank MM. Complement 1 inhibitor is a regulator of the alternative complement pathway. J Exp Med 2001;194:1609–1616. [PubMed: 11733575]

Karpel-Massler G, Fleming SD, Kirschfink M, Tsokos GC. Human C1 esterase inhibitor attenuates murine mesenteric ischemia/reperfusion induced local organ injury. J Surg Res 2003;115:247–256. [PubMed: 14697291]

Kerr FK, Thomas AR, Wijeyewickrema LC, Whisstock JC, Boyd SE, Kaiserman D, Mathews AY, Bird PI, Thielens NM, Rossi V, Pike RN. Elucidation of the substrate specificity of the MASP-2 protease of the lectin complement pathway and identification of the enzyme as a major physiological target of the serpin, C1-inhibitor. Mol Immunol 2008;45:670–677. [PubMed: 17709141]

Landerman NS, Webster ME, Becker EL, Ratcliffe HE. Hereditary angioneurotic edema. II. Deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein. J Allergy 1962;33:330–341. [PubMed: 14461960]

Lathem WW, Bergsbaken T, Welch RA. Potentiation of C1 esterase inhibitor by StcE, a metalloprotease secreted by Escherichia coli O157:H7. J Exp Med 2004;199:1077–1087. [PubMed: 15096536]

Lathem WW, Grys TE, Witowski SE, Torres SE, Kaper JB, Tarr PI, Welch RA. StcE, a metalloprotease secreted by Escherichia coli O157:H7, specifically cleaves C1 esterase inhibitor. Mol Microbiol 2002;45:277–288. [PubMed: 12123444]

Laurell AB, Martensson U, Sjoholm AG. C1 subcomponent complexes in normal and pathological sera studied by crossed immunoelectrophoresis. Acta Pathol Microbiol Scand 1976;84:455–464.

Lauterbach M, Horstick G, Plum N, Lotz J, Lauterbach E, Weilemann LS, Kempski O. C1-esterase inhibitor reverses functional consequences of superior mesenteric artery ischemia/reperfusion by

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limiting reperfusion injury and restoring microcirculatory perfusion. Shock 2007;27:75–83. [PubMed: 17172984]

Lehmann C, Birnbaum J, Luhrs C, Ruckbeil O, Spies C, Ziemer S, Grundling M, Pavlovic D, Usichenko T, Wendt M, Kox WJ. Effects of C1 esterase inhibitor administration on intestinal functional capillary density, leukocyte adherence and mesenteric plasma extravasation during experimental endotoxemia. Intensive Care Med 2004;30:309–314. [PubMed: 14586496]

Lehmann TG, Heger M, Munch S, Kirschfink M, Klar E. In vivo microscopy reveals that complement inhibition by C1-esterase inhibitor reduces ischemia/reperfusion injury in the liver. Transpl Int 2000;13:S547–S550. [PubMed: 11112070]

Liu D, Cai S, Gu X, Scafidi J, Wu X, Davis AE III. C1 inhibitor prevents endotoxin shock via a direct interaction with lipopolysaccharide. J Immunol 2003;171:2594–2601. [PubMed: 12928411]

Liu D, Cramer CC, Scafidi J, Davis AE III. N-linked glycosylation at Asn3 and the positively charged residues within the amino terminal domain of C1 inhibitor are required for its interaction with Salmonella typhimurium lipopolysaccharide and lipid A. Infect Immun 2005a;73:4478–4487. [PubMed: 16040958]

Liu D, Gu X, Scafidi J, Davis AE III. N-linked glycosylation is required for C1 inhibitor-mediated protection from endotoxin shock in mice. Infect Immun 2004;72:1946–1955. [PubMed: 15039314]

Liu D, Lu F, Qin G, Fernandes SM, Li J, Davis AE III. C1 inhibitor-mediated protection from sepsis. J Immunol 2007;179:3966–3972. [PubMed: 17785834]

Liu D, Zhang D, Scafidi J, Wu X, Cramer CC, Davis AE III. C1 inhibitor prevents gram negative bacterial lipopolysaccharide-induced vascular permeability. Blood 2005b;72:1946–1955.

Marr N, Luu RA, Fernandes RC. Bordetella pertussis binds human C1 esterase inhibitor during the virulent phase, to evade complement-mediated killing. J Infect Dis 2007;195:585–588. [PubMed: 17230419]

Matsunami K, Miyagawa S, Yamada M, Yoshitatsu M, Shirakura R. A surface-bound form of human C1 esterase inhibitor improves xenograft rejection. Transplantation 2000;69:749–755. [PubMed: 10755521]

Matsushita M, Thiel S, Jensenius JC, Terai If T. Proteolytic activities of two types of mannose-binding lectin associated serine protease. J Immunol 2000;165:2637–2642. [PubMed: 10946292]

McConnell DJ. Inhibitors of kallikrein in human plasma. J Clin Invest 1972;51:1611–1623. [PubMed: 4113391]

Nielsen EW, Mollnes TE, Harlan JM, Winn RK. C1-inhibitor reduces the ischaemia-reperfusion injury of skeletal muscles in mice after aortic cross-clamping. Scand J Immunol 2002;56:588–592. [PubMed: 12472670]

Padilla ND, van Vliet AK, Schoots IG, Seron MV, Maas MA, Peltenburg EE, de Vries A, Niessen HW, Hack CE, Van Gulik TM. C-reactive protein and natural IgM antibodies are activators of complement in a rat model of intestinal ischemia and reperfusion. Surgery 2007;142:722–733. [PubMed: 17981193]

Patston PA, Schapira M. Regulation of C1-inhibitor function by binding to type IV collagen and heparin. Biochem Biophys Res Commun 1997;230:597–601. [PubMed: 9015369]

Petersen SV, Thiel S, Jensen L, Vorup-Jensen T, Koch C, Jensenius JC. Control of the classical and the MBL pathway of complement activation. Mol Immunol 2000;37:803–811. [PubMed: 11257302]

Pixley RA, De La Cadena R, Page JD, Kaufman N, Wyshock EG, Chang A, Taylor FB Jr, Colman RW. The contact system contributes to hypotension but not disseminated intravascular coagulation in lethal bacteremia. In vivo use of a monoclonal anti-factor XII antibody to block contact activation in baboons. J Clin Invest 1993;91:61–68. [PubMed: 7678610]

Poling J, Oezkur M, Kogge K, Mengel M, Niemann H, Winkler M, Haverich A, Wiebe K. Hyperacute rejection in ex vivo-perfused porcine lungs transgenic for human complement regulatory proteins. Trans Int 2006;19:225–232.

Przemek M, Lorenz R, Vangerow B, Klempnauer J, Winkler M, Piepenbrock S. Pretreatment with C1-esterase inhibitor improves cardiovascular stability in small primates undergoing porcine kidney xenotransplantation. Transplant Proc 2002;34:2383. [PubMed: 12270448]

Ranby M, Bergstorf N, Nilsson T. Enzymatic properties of one and two chain forms of tissue plasminogen activator. Thromb Res 1982;27:175–184. [PubMed: 6890245]

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Ratnoff O, Lepow I. Some properties of an esterase derived from preparations of the first component of complement. J Exp Med 1957;106:327–343. [PubMed: 13449241]

Ratnoff O, Pensky J, Ogston D, Naff G. The inhibition of plasmin, plasma kallikrein, plasma permeability factor, and the C1'r subcomponent of complement by serum C1' esterase inhibitor. J Exp Med 1969;129:315–331. [PubMed: 4178758]

Sainz IM, Pixley RA, Colman RW. Fifty years of research on the plasma kallikrein-kinin system: From protein structure and function to cell biology and in-vivo pathophysiology. Thromb Haemost 2007;98:77–83. [PubMed: 17597995]

Salvatierra A, Velasco F, Rodriguez M, Alvarez A, Lopez-Pedrera R, Ramirez R, Carracedo J, Lopez-Rubio F, Lopez-Pujol A, Guerrero R. C1-esterase inhibitor prevents early pumonary dysfunction after lung transplantation in the dog. Am J Respir Crit Care Med 1997;1997:1147–1154. [PubMed: 9117001]

Schapira M, Despland E, Scott CF, Boxer LA, Colman RW. Purified human plasma kallikrein aggregates human neutrophils. J Clin Invest 1982;69:1199–1202. [PubMed: 6917855]

Schelzig H, Simon F, Krischer C, Vogel A, Abendroth D. Ex-vivo hemoperfusion (eHPS) of pig-lungs with whole human blood: effects of complement inhibition with a soluble C1-esterase-inhibitor. Ann Transplant 2001;6:34–39. [PubMed: 11899895]

Scherer RU, Giebler RM, Schmidt U, Paar D, Kox WJ. The influence of C1-esterase inhibitor substitution on coagulation and cardiorespiratory parameters in an endotoxin-induced rabbit model of hypercoagulability. Seminars in Thrombosis & Hemostasis 1996;22:357–366. [PubMed: 8944422]

Schmaier AH. Assembly, activation, and physiologic influence of the plasma kallikrein/kinin system. Int Immunopharmacol 2007;8:161–165. [PubMed: 18182220]

Schmidt W, Stenzel K, Walther A, Gebhard MM, Martin E, Schmidt H. Influence of C1-esterase inhibitor on tissue oxygenation of jejunal mucosa during endotoxemia. Int J Surg Investig 1999a;1:277–283.

Schmidt W, Stenzel Z, Gebhard MM, Martin E, Schmidt H. C1-esterase inhibitor and its effects on endotoxin-induced leukocyte adherence and plasma extravasation in postcapillary venules. Surgery 1999b;125:280–287. [PubMed: 10076612]

Schroder C, Wu GS, Price E, Johnson JE, Pierson RNr, Azimzadeh AM. Hyperacute rejection of mouse lung by human blood: characterization of the model and the role of complement. Transplantation 2003;76:755–760. [PubMed: 14501848]

Siebeck M, Philapitsch A, Wiesinger H, Welter HF. C1-esterase in early septicemia. Prog Clin Biol Res 1987;236A:141–147. [PubMed: 2441404]

Sim RB, Arlaud GJ, Colomb MG. C1 inhibitor dependent dissociation of human complement component C1 bound to immune complexes. Biochem J 1979a;179:449–457. [PubMed: 475762]

Sim RB, Reboul A, Arlaud GJ, Villiers CL, Colomb MG. Interaction of 125I-labelled complement components C1r and C1s with protease inhibitors in plasma. FEBS Lett 1979b;97:111–115. [PubMed: 761607]

Storini C, Rossi E, Marrella V, Distaso M, Veerhuis R, Vergani C, Bergamaschini L, De Simoni MG. C1-inhibitor protects against brain ischemia-reperfusion injury via inhibition of cell recruitment and inflammation. Neurobiol Dis 2005;19:10–17. [PubMed: 15837556]

Strachan AJ, Woodruff TM, Haaima G, Fairlie DP, Taylor SM. A new small molecule C5a receptor antagonist inhibits the reverse-passive Arthus reaction and endotoxic shock in rats. J Immunol 2000;164:6560–6565. [PubMed: 10843715]

Struber M, Hagl C, Hirt SW, Cremer J, Harringer W, Haverich A. C1-esterase inhibitor in graft failure after lung transplantation. Intensive Care Med 1999;25:1315–1318. [PubMed: 10654221]

Sulikowski T, Patston PA. The inhibition of TNK-t-PA by C1-inhibitor. Blood Coagul Fibrinolysis 2001;12:75–77. [PubMed: 11229830]

Takada M, Nadeau KC, Shaw GD, Marquette KA, Tilney NL. The cytokine-adhesion molecule cascade in ischemia/reperfusion injury of the rat kidney. Inhibition by a soluble P-selectin ligand. J Clin Invest 1997;99:2682–2690. [PubMed: 9169498]

Thielmann M, Marggraf G, Neuhauser M, Forkel J, Herold U, Kamler M, Massoudy P, Jakob H. Administration of C1-esterase inhibitor during emergency coronary artery bypass surgery in acute ST-elevation myocardial infarction. Eur J Cardiothorac Surg 2006;30:285–293. [PubMed: 16829095]

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Toomayan GA, Chen LE, Jiang HX, Qi WN, Seaber AV, Frank MM, Urbaniak JR. C1-esterase inhibitor and a novel peptide inhibitor improve contractile function in reperfused skeletal muscle. Microsurgery 2003;23:561–567. [PubMed: 14705072]

van der Graaf F, Koedam JA, Bouma BN. Inactivation of kallikrein in human plasma. J Clin Invest 1983;71:149–158. [PubMed: 6184384]

Vangerow B, Hecker JM, Lorenz R, Loss M, Przemeck M, Appiah R, Schmidtko J, Jalali A, Rueckoldt H, Winkler M. C1-inhibitor for treatment of acute vascular xenograft rejection in cynomogus recipients of h-DAF transgenic porcine kidneys. Xenotransplantation 2001;8:266–272. [PubMed: 11737852]

Wu G, Pfeiffer S, Schroder C, Zhang T, Nguyen BN, Kelishadi S, Atkinson JB, Schuurman HJ, White DJ, Azimadeh AM, Pierson RNr. Coagulation cascade activation triggers early failure of pig hearts expressing human complement regulatory genes. Xenotransplantation 2007;14:34–37. [PubMed: 17214703]

Zeerleder S, Caliezi C, Van Mierlo G, Eerenberg-Belmer A, Sulzer I, Hack CE, Wuillemin WA. Administration of C1 inhibitor reduces neutrophil activation in patients with sepsis. Clin Diagn Lab Immunol 2003;10:529–535. [PubMed: 12853381]

Ziccardi R. Demonstration of the interaction of native C1 with monomeric immunoglobulins and C1 inhibitor. J Immunol 1985;134:2559–2563. [PubMed: 3973388]

Ziccardi RJ. Activation of the early components of the classical complement pathway under physiological conditions. J Immunol 1981;126:1768–1773.

Ziccardi RJ, Cooper NR. Active disassembly of the first complement component C1 by C1-inhibitor. J Immunol 1979;123:788–792. [PubMed: 110880]

Zwijnenburg PJG, van der Poll T, Florquin S, Polfliet MMJ, van den Berg TK, Dijkstra CD, Roord JJ, Hack CE, van Furth AM. C1 inhibitor treatment improves host defense in pneumococcal meningitis in rats and mice. J Infect Dis 2007;196:115–123. [PubMed: 17538891]

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Table 1

C1 INHIBITOR ACTIVITIES	
Protease Inhibition	
Complement system	C1r, C1s, MASP2
Plasma kallikrein-kinin system	plasma kallikrein, factor XII
Fibrinolytic system	plasmin, tissue plasminogen activator
Coagulation system	factor XI, thrombin
Interactions with Endogenous Proteins	
Complement system	C3b
Extracellular matrix	type IV collagen, laminin, entactin, fibrin
Interactions with Cells	
Circulating cells	neutrophils, macrophages
Vascular cells	endothelial cells
Interactions with Infectious Agents	
Endotoxin	*E. coli* 011:B4, *E. coli* 0127:B8, *E. coli* 055:B5, *E. coli* K-235, *Salmonella typhimurium, Salmonella minnesota, Salmonella typhosa*
Bacteria	*Bordetella pertussis, E. coli, Serratia marcescens*
Parasites	*Plasmodium falciparum*