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The deficiency of C1 inhibitor and its treatment

Marco Cicardi*, Lorenza C. Zingale*

Department of Internal Medicine, University of Milan, San Giuseppe Hospital A.Fa.R., Milan, Italy

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Abstract

In this article, we review the traditional therapies of hereditary angioedema (HAE) that have been used for several years. Some of these therapies were proposed before the definition of the underlying defect and the understanding of the pathogenesis of the disease. We also describe new compounds under investigation at present as potential therapies for HAE. Two of these new therapies (a plasma-kallikrein inhibitor and a bradykinin B(2)-receptor antagonist) have been developed based on the understanding that the pathogenesis of symptoms was mainly due to kallikrein activation and bradykinin release.
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Keywords: C1 inhibitor; Hereditary angioedema; Dx-88; Icatibant; Danazol; Tranexamic acid

Introduction

A number of review articles covering the topic of the biology of C1 inhibitor (C1-INH), its deficiency states and its potential use as a therapeutic have appeared in the last 5 years (Agostoni et al., 2004; Bergamaschini and Cicardi, 2003; Bos et al., 2002; Bowen et al., 2004; Cicardi et al., 2005; Davis, 2004, 2005; Frank, 2004a, b; Gompels and Lock, 2005; Rosen and Davis, 2005; Zuraw, 2005). Therefore, we will focus the present review on the therapy of this deficiency state and the potential changes that may appear in the near future as a result of the several clinical trials going on at present both to renew the files of established treatments as well as to evaluate new compounds.

Patients suffering from C1-INH deficiency are exposed to angioedema a reversible, self-limiting edema of the deeper cutaneous and mucosal layers (Agostoni et al., 2004). The pathogenetic mechanisms that translate the stable deficiency of C1-INH into a transient increase in vascular permeability have been a matter of debate for a long time, also in view of the fact that the multiple inhibitory activities of this serin protease inhibitor (Serpin) allows different hypotheses (Davis, 2003).

C1-INH, in fact, controls activation of the complement system by inhibiting the esterase activities of C1r and C1s in the classical pathway and of MASP 2 in the lectin pathway (Davis, 2004). In deficient patients, these proteases are not properly controlled and consume their substrates, C4 and C2, the level of which is reduced in plasma. The second major physiological role of C1-INH is regulation of the contact system where it intervenes inhibiting activated coagulation factor XII (fXII) and active kallikrein (KK). Although no changes in plasma levels of the components of this system are detectable in deficient patients, signs of hyperactivation are

*Corresponding authors. Tel.: +39 028599 4494; fax: +39 028599 4157.
E-mail addresses: Marco.Cicardi@unimi.it (M. Cicardi), Lorenza.Zingale@unimi.it (L.C. Zingale).

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clearly present when these patients develop angioedema (Cullmann et al., 1982). In addition to the control of complement and contact systems activation, C1-INH inhibits factor XI, plasmin and tissue plasminogen activator (tPA) although the relevance of these activities, in vivo, remains controversial.

Going back to the pathogenesis of angioedema in C1-INH deficiency, it is now well accepted that bradykinin (BK), released upon contact system activation, is the main mediator of the increase in vascular permeability. Early experiments favouring contact system activation as a key event for hereditary angioedema (HAE) symptoms (Curd et al., 1980; Fields et al., 1983; Schapira et al., 1983) have been confirmed by the evidence that BK is increased in patients plasma during attacks (Nussberger et al., 1998) and that blocking BK activity and/or its release reverted the increased vascular permeability that characterizes C1-INH K.O. mice (Han et al., 2002).

HAE symptoms are a local phenomenon initiated by a triggering event (the best identified is trauma, but many others not jet defined may have a similar effect) that exposes negative charges on the endothelial cell surface. FXII and prekallikrein (PK) activate each other on negatively charged surfaces. High molecular weight kininogen (HK), a pivotal protein for assembly of contact system protein on cell surface, augments the reciprocal activation of fXII and PK and the zymogen PK becomes activated to KK when it binds HK on endothelial cells (Caliezi et al., 2002; Kaplan et al., 2002). Endothelial cell-bound active KK amplifies contact system activation, being a major activator of fXII, and releases BK by cleaving HK at two sites and creating a positive amplification loop that allows initial conversion of fXII into its active form fXIIa. Summarizing, HAE patients experience angioedema because of a defective control of the plasma kinin-forming cascade which is activated by contact with negatively charged macromolecules leading to binding and autoactivation of fXII, activation of PK to KK by fXIIa, and cleavage of HK by KK to release the vasoactive peptide BK (Fig. 1). There is no straight route to reconciling this series of events with early experiments that regarded complement and fibrinolytic systems as central to the pathogenesis of angioedema. A role for plasmin, considered essential to the generation of the vasoactive peptide (Donaldson et al., 1977), remains feasible since it is generated from plasminogen upon contact system activation and facilitates KK-mediated release of BK from HK (Kleniewski et al., 1992). Nevertheless, this scenario does not endorse a significant role for complement, unlike the evidence brought by experiments performed between the late 1960s and early 1770s (Donaldson and Rosen, 1964; Donaldson, 1968, 1969;Donaldson et al., 1969). Whether this is a definitive achievement cannot be concluded at present.

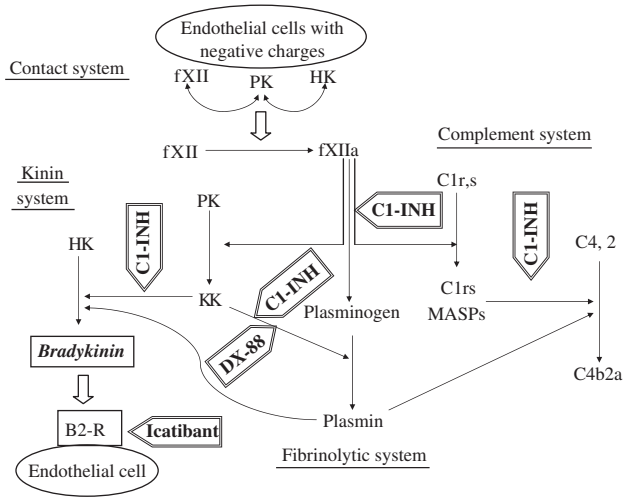

Fig. 1. FXII, PK and HK activate each other on the endothelial cell surface that exposes negative charges. The activation of these zymogens leads to the formation of enzymatically active components in the kinin, complement and fibrinolytic systems and to the release of the vasoactive peptide BK which binds to its B2 receptors on the cell surface eventually resulting in an increase in vascular permeability. C1-INH either plasma derived or recombinant blocks at different levels these reactions while Icatibant and Dx-88 have specific sites of action.

The therapy of angioedema due to C1-INH deficiency

Attempts to cure patients with HAE started before the definition of the underlying defect and the understanding of its pathogenesis. Among these reports, particular emphasis is owed to the use of methytestosterone that Spaulding (1960) demonstrated to be clearly superior to placebo for preventing angioedema in HAE patients. In order to provide explanation for such an effect, based on the unpublished observation of Professor Sylvia Bensley that testosterone protects male guinea pigs from some of the effects of histamine, Spaulding speculated that HAE patients could produce excessive amounts of histamine or hyaluronidase in response to slight injury. Sixteen years later revisiting this approach, the group of M. Frank (Gelfand et al., 1976) at the NIH using danazol confirmed the high efficacy of androgen derivatives for prophylaxis of HAE symptoms and showed that this drug was also able to revert the underlying biochemical defect. The last 30 years have seen a tremendous growth of the use of androgen derivatives in HAE. Different preparations were shown to be effective, the requisite being alkylation at position 17 alpha, and the large clinical experience accumulated with danazol and stanozolol suggest a relatively favourable safety profile on long term use (Agostoni et al., 1980a; Cicardi et al., 1983, 1991, 1997; Sheffer et al., 1981, 1987; Szeplaki et al., 2005). Nevertheless,

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