EDITORIAL

Oxidative stress in hereditary angioedema caused by C1 inhibitor deficiency: an interesting finding that deserves further studies

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by Obtułowicz et al, see p. 79

Recurrent angioedema is a clinical syndrome characterized by bouts of skin, cutaneous, and submucosal tissue swelling or by edema located at upper respiratory sites (or both). Nonallergic angioedema without wheals is defined as primary angioedema. The current classifications recognize different forms of hereditary angioedema (HAE), such as those caused by a deficiency of complement component 1 esterase inhibitor (C1-INH-HAE), those with normal C1-INH and coagulation factor XII (FXII) mutations (FXII-HAE), and those with normal C1-INH and another specific (angiopoietin-1-HAE, plasminogen-HAE, kininogen-1-HAE) or unknown (U-HAE) genetic cause.[1] The primary pathophysiologic mechanism is a complex disorder of vascular permeability, primarily due to contact system activation, which triggers FXII protein into its active form FXIIa, and this in turn can activate kallikrein and bradykinin, leading to angioedema. The overproduction of bradykinin and other endothelial mediators, such as vascular permeability factors including vascular endothelial growth factors (VEGFs) and angiopoietins, may exert its effects not only on the vascular leak.

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Obtułowicz et al[2] report a significant increase in basal and hydrogen peroxide–induced levels of reactive oxygen species (ROS) in a group of patients with C1-INH-HAE, as well as an antioxidant action of exogenous bradykinin on both these phenomena.[2] This study confirms and expands the recent finding of enhanced oxidative stress, as measured by circulating levels of advanced oxidation protein products (AOPPs) and advanced glycation end products, in the C1-INH-HAE and FXII-HAE subtypes of the disease during the remission period.[3]

It is worth noting that the main known effects of bradykinin in HAE have been extensively studied in the endothelium and not in peripheral blood mononuclear cells (PBMCs). Obtułowicz et al[2] found a different and unanticipated response to exogenous bradykinin in the redox status in patients compared with healthy controls.

While the cellular redox buffer systems tightly control the concentrations of ROS, if produced in excess, they may contribute to vascular disease, in which superoxide anion has been demonstrated to inactivate nitric oxide (NO) and thereby contribute to endothelial dysfunction.[4] Our research group also demonstrated the presence of an underlying endothelial dysfunction in HAE patients by using peripheral artery tonometry and serum asymmetric dimethylarginine levels (a strong inhibitor of NO synthesis [NOS]).[5] Those markers are already well established and crucial for cardiovascular risk stratification.[6]

The binding and activation of two G protein–coupled receptors mediate the kinin involvement in inflammatory process. Bradykinin B_1 receptor (B_1R) is induced by proinflammatory milieu including cytokines and oxidative stress through the transcriptional nuclear factor κ-light-chain-enhancer of activated B cells, while bradykinin B_1 receptor (B_2R) is constitutively expressed in the endothelium and plays a major role in increasing vascular permeability.[3,7] Bradykinin B_1 receptor is a powerful activator of inducible NOS and NADPH oxidase, which are associated with vascular inflammation, increased vascular leakage, and endothelial dysfunction.[7] When engaged, both B_1R and B_2R mediate vasodilation and an increase in permeability, leading to the activation of G proteins (in particular, Gαq) and downstream pathways of signaling, including endothelial NOS (eNOS), phospholipase A_2 (PLA_2), and phospholipase C-β_1.[7] Secreted PLA_2 enzymatic activity is increased in patients with C1-INH-HAE, in whom it has been shown to promote vascular permeability and to impair C1-INH activity, and also to induce

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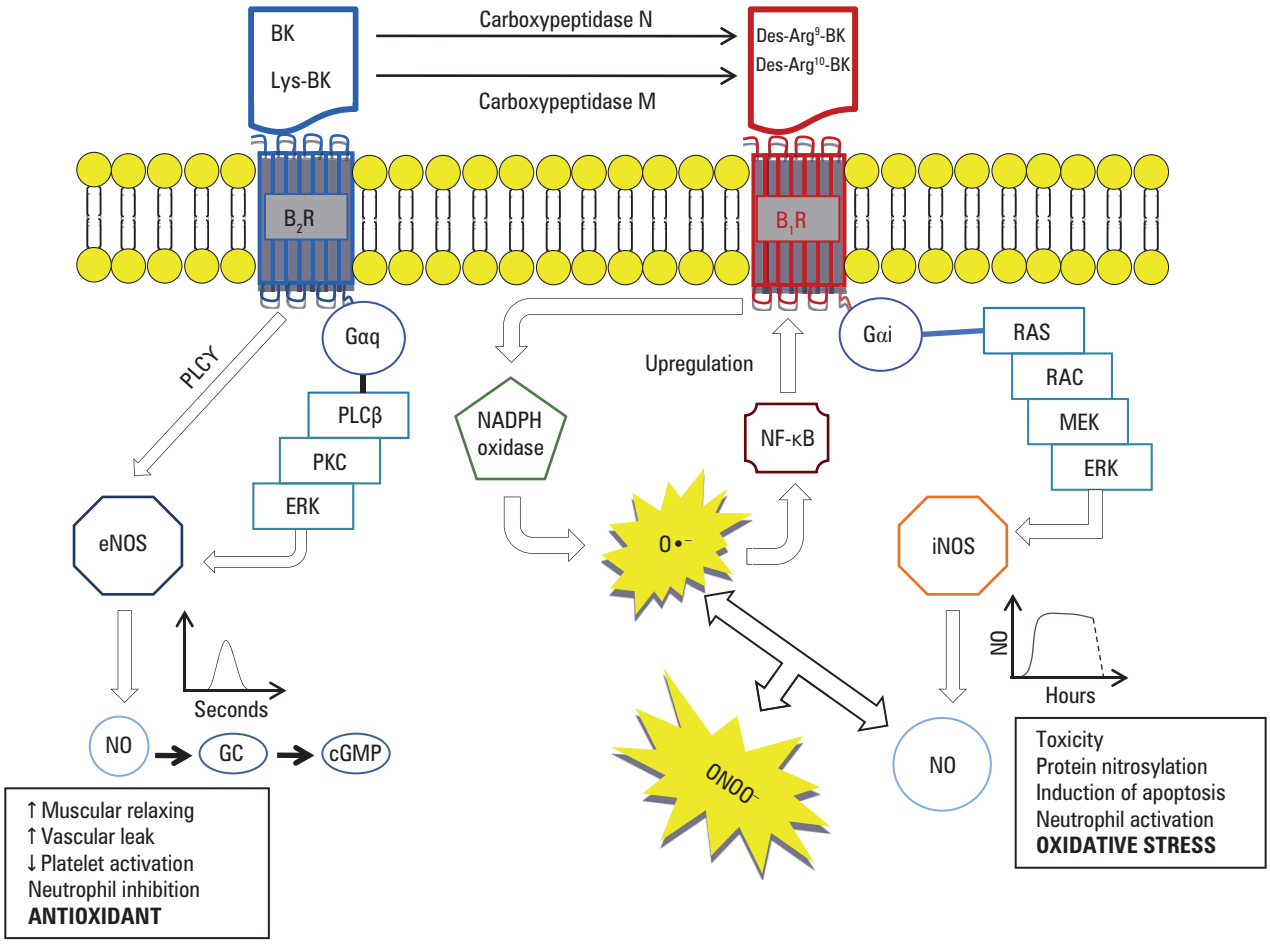

FIGURE 1 Bradykinin receptors and oxidative stress: second messengers and physiological effects; bradykinin B_1 and B_2 receptors and their mutual effect on redox balance

Abbreviations: ↓, decreased; ↑, increased; BK, bradykinin; B_1R, bradykinin B_1 receptor; B_2R, bradykinin B_2 receptor; cGMP, cyclic guanosine monophosphate; Des-Arg^9-BK, des-Arg^9-bradykinin metabolite; Des-Arg^{10}-BK, des-Arg^{10}-kallidin metabolite; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; Gαi, subunit α inhibitor of G protein; Gαq, subunit α of G protein; GC, guanylate cyclase; iNOS, inducible nitric oxide synthase; LysBK, lysyl-bradykinin; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NO, nitric oxide; MEK, mitogen activated protein kinase kinase; PKB, phosphokinase B; PKC, phosphokinase B; PLC, phospholipase C; RAC, RAS-related C3 botulinum toxin substrate 1; RAS, rat sarcoma guanine-nucleotide-binding protein

the release of proangiogenic and antiangiogenic factors by neutrophils.[8] Secreted PLA_2 activity showed no differences between patients with FXII-HAE, U-HAE, and angiopoietin-1-HAE,[9] and in our opinion, it would be interesting to explore its correlation with redox balance in patients with HAE. It is well known that B_2R has a protective role in oxidative stress–related disorders of the kidney and heart[10] through eNOS induction and an increased transient NO production. The activation of PLA_2 may lead to the formation of prostaglandins, accumulation of cyclic adenosine monophosphate, and reduction of ROS generation.[11] Increased eNOS levels during remission have been reported in patients with C1-INH-HAE,[12] together with the evidence of coronary endothelial dysfunction.

Obtułowicz et al[2] showed that PBMCs are a relevant source of ROS generation ex vivo. However, further research is needed to investigate the main cellular types involved in this finding and the potential role of kinin receptor expression and signalling in patients with HAE.[13] Differences in the effects of bradykinin receptors have been extensively investigated, with human studies focusing mostly on the endothelium.[7]

Besides the B_2R-like pathways, B_1R activates Gαq and Gαi, leading to a prolonged signaling and to signaling through inducible NOS activation, which generates a much higher and prolonged NO output with the potential to promote inflammatory response.[14] High NO levels can react with superoxide anion, leading to higher peroxynitrite generation and to a higher oxidative stress burden in mice. However, no data about protein nitrosylation are yet available for patients with HAE. Furthermore, the involvement of B_1R enhances oxidative stress levels, at the same time activating the NADPH oxidase complex, thus resulting in an increased generation of superoxide anion in human cells and murine model (FIGURE 1).[15]

Further studies are needed to better define the effects of oxidative stress on endothelial receptors as well as complement, contact, and plasminogen systems involved in the pathophysiology of HAE. Given the abundant expression of

the receptors of those systems in PBMCs, their role is intriguing and largely unexplored. Also, the oxidation of fibrinogen is interesting, as it is known to have a pivotal role in the formation of AOPPs and may, in turn, cause functional alterations in fibrinogen or its fragments, possibly leading to altered procoagulant activity or modifying its direct effects on vascular permeability.[3] Speculatively, it should be relevant to evaluate whether higher oxidative stress can induce a state of "vascular preconditioning," similarly to VEGFs and angiopoietins,[8] that may predispose or reduce angioedema attacks.

Even if the main cause of death among HAE patients has previously been upper airway edema with asphyxiation (20%–30% of C1-INH-HAE patients when treatments were not available), the efficacy of current treatments has resulted in a considerable decrease in mortality (0.35%–0.5% in appropriately treated patients) and more patients reaching older age. In this respect, since enhanced oxidative stress, endothelial dysfunction, and atherosclerosis are intertwined in a complex process that involves several mechanisms and is recognized as the leading cause of heart attacks myocardial infarction, stroke, and peripheral vascular disease,[4] we envisage further studies in HAE patients to clarify this issue. Also, studies investigating the actual incidence of ischemic heart disease and stroke in HAE are warranted. Finally, the potential correlation of oxidative stress status with clinical and laboratory biomarkers of HAE should be further analyzed in multicenter studies enrolling adequately powered cohorts of patients with this rare disease, which might provide valuable insights into this topic.

ARTICLE INFORMATION

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