Bradykinin B2 Receptor Agonism: A Novel Therapeutic Strategy for Myocardial Infarction?

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In 2000, the Heart Outcomes Prevention Evaluation (HOPE) clinical trial demonstrated the efficacy of angiotensin-converting enzyme (ACE) inhibition in reducing the rates of acute myocardial infarction and stroke in high-risk patients. Angiotensin II plays a major role in cardiovascular disease and its diminution by ACE inhibition is thought to directly improve primary cardiovascular outcome. However, ACE also actively participates in the regulation of the kallikrein-kinin system by degrading bradykinin and generating inactive metabolites. In this regard, an augmentation of bradykinin may also explain the beneficial effects of ACE inhibition in the context of acute myocardial infarction. Bradykinin is a nonapeptide, which is derived from protein precursors called kininogens, through the action of the kallikreins. Transgenic rats overexpressing tissue kallikrein, are protected against myocardial infarction-induced damage, and exhibit improved cardiac remodeling. These cardioprotective effects are mediated by the activation of the B2 receptor because they are inhibited by the specific B2 antagonist icatibant (HOE140). Furthermore, we could recently show that transgenic rats overexpressing B2 receptors exclusively in cardiomyocytes show improved cardiac functions and are protected from cardiac damage induced by pressure overload (M. Bader, M. Barbosa, and J.B. Pesquero, unpublished data). The use of agonists of the B2 receptor may therefore be beneficial in cardiac diseases. Accordingly, in this issue of the American Journal of Hypertension, Marketou et al. report about the therapeutic effects of a newly developed bradykinin B2 receptor agonist reducing tissue damage and improving cardiac remodeling in acute myocardial infarction. Their evidence is based on extensive histological and physiological measurements including infarct size, ejection fraction, fractional shortening and systolic blood pressure analyses. The well-described local vasodilatory and antifibrotic properties of the B2 receptor as well as the B2-induced facilitation of glucose metabolism are probably responsible for these effects. However, the authors mainly explain their results by ant apoptotic and anti-inflammatory properties of the B2 receptor based on decreased terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining and a diminished expression of the proinflammatory marker, tumor necrosis factor-α, respectively. Clearly, more detailed studies are warranted to elucidate the mechanism of the beneficial actions of the new drug. Moreover, a more comprehensive characterization of the newly developed B2 agonist, in particular regarding its selectivity in vivo, will be necessary. In any case, B2 receptor activation is a therapeutic strategy which should be considered with caution because this receptor is involved in nociception and hyperalgesia and its activation in nerve endings of C-fibers is accompanied by one of the strongest painful sensations known. Furthermore, a plethora of proinflammatory actions have been ascribed to the B2 receptor such as activation of cyclooxygenase-2 and endothelial permeabilization.

In summary, Gavras and colleagues importantly confirmed that the activation of the B2 receptor reduces tissue damage and improves cardiac remodeling. Thereby, the authors put forward the therapeutic value of B2 receptor agonism. However, the mechanism of action and, even more importantly, the possible risks of this interesting new pharmaceutical strategy merit further exploration.

Disclosure: The authors declared no conflict of interest.


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doi:10.1038/ajh.2010.32

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