Animal Model

Animal model for endotoxic shock: transgenic rats with endothelial overexpression of kinin B1 receptors

Reference Number 03-00300

Abstract

Challenge

Kinins are important peptide mediators of a diverse range of physiological and pathological functions of the cardiovascular system and exert their effects by selective activation of two receptors termed B1 and B2. The B1 receptor is activated by metabolites, the synthesis of which are increased during inflammation. The initiation of an endotoxic shock is characterized by two hypotensive phases where recent data have shown that the B1 receptor may play an important role in modulation of vascular tone, plasma extravasation, and leukocyte migration into inflamed tissue. An appropriate animal model for the functional analysis of B1 receptor in the endothelium is lacking.

Technology

Therefore, a transgenic rat TGR(Tie2B1) with endothelial cell-specific kinin B1 receptor overexpression was generated to determine mediators and signalling mechanisms employed by B1 receptors in endothelial cells.
Endotoxin/lipopolysaccharide (LPS) is the major mediator that triggers the cellular and humoral responses of endotoxic shock induced by Gram-negative bacteria. To test if B1 receptor expression in endothelial cells is relevant for endotoxin-induced hypotension Tie2B1 rats were treated with B1 agonist. The rats are normotensive but responded to B1 agonist treatment with a decrease in blood pressure and increased plasma extravasation but were otherwise inconspicuous. However, after LPS treatment they presented a more pronounced hypotensive response and marked brady-cardia associated with increased mortality (Figure 1) when compared to non-transgenic control animals. The endothelial cell-specific expression was confirmed by B1 agonist-induced relaxation of isolated aortae, which was abolished by endothelial denudation of the vessel. This vasodilation was mediated by nitric oxide and K+ channels. Thus, the endo-thelial kinin B1 receptor plays an important role in the initiation of endotoxic shock and may be a valid pharmacological target in cardiovascular diseases. In addition, the generated transgenic rats offer a valid model to test drugs important for the treatment of sepsis.

Commercial Opportunity

Tie2B1 mice present the first in vivo model of constitutive and functional B1 receptor expression restricted to the vasculature. Breeding pairs of TGR(Tie2B1) rats are available under Tangible Property Licence Agreement.

Patent Situation

No patent application has been filed.

Further Reading

- Merino et al., J Mol Med (2008), 86:791-798
- Bader, Arterioscler Thromb Vasc Biol. 2009 May;29(5):617-9.

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