Ca^{2+}-SENSING RECEPTORS IN BLOOD VESSELS : POTENTIAL NEW TARGETS IN VASCULAR DISEASE

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The benefits of reducing blood pressure in the prevention of cardiovascular complications are well-established. However, despite the variety of approaches to the treatment of hypertension (beta-blockers, diuretics, ACE inhibitors, calcium-antagonists) and the use of combination therapy, a reduction in blood pressure is not always achieved. Thus, further research into novel pharmacological approaches is warranted. An extracellular calcium-sensing receptor (CaR), recently discovered in vascular endothelial cells, may provide an alternative target for the therapeutic control of hypertension. The parathyroid CaR plays an important role in calcium homeostasis and both positive and negative allosteric modulators of the receptor (calcimimetics and calcilytics, respectively) have been developed for the treatment of hyperparathyroidism and osteoporosis, respectively. The use of these drugs to activate or inhibit the CaR has provided clues to the physiological role of this receptor in tissues which are not involved in Ca^{2+} homeostasis. In the rat mesenteric artery, calcimimetics produce an endothelium-dependent reduction in vascular tone. This appears to result from the selective opening of one type of endothelial K^+ channel, the intermediate-conductance calcium-sensitive K^+ channel (IK_{Ca}). The opening of this channel leads to hyperpolarization which (in mesenteric resistance arteries) is transferred electrotonically to the myocytes. In addition, the K^+ ions which move out of the endothelium have direct effects on the myocyte which also contribute to their hyperpolarization. Although this calcimimetic effect has been assumed to be due to activation of the CaR, a receptor closely related to the CaR (GPRC6A) is activated by NPS R-568, a positive allosteric modulator of CaR. Both the CaR and the GPRC6A are not only sensitive to extracellular Ca^{2+} (and the allosteric modulators) but are also activated by amino acids. Thus, their physiological role may provide the link between protein digestion and post-prandial hyperaemia. Whether the vasorelaxant effect of the calcimimetic results from activation of CaR or GPRC6A, either individually or in heteromeric combination, remains to be established. Irrespective of this, modulation of an endothelial G-protein-coupled receptor, which may function to regulate vascular tone, provides a novel and exciting new approach for the control of hypertension.