KALLIKREINS AS TARGETS FOR MEDICAL APPLICATION

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Authentic kallikreins originally defined as blood pressure decreasing or kinin liberating enzymes are proteases with very restricted substrate specificity. Tissue kallikreins are involved via kinin liberation in various physiological functions (e.g. blood pressure regulation, glucose uptake in working muscle cells) but also in pathological processes (e.g. edema formation, pain generation). Plasma kallikrein is involved besides in kinin generation also in the intrinsic clotting cascade and in stimulation of inflammatory cells. More recently tissue kallikrein-like multigene families have been described in humans and rodents. Besides authentic tissue kallikrein 14 of the 15 kallikrein gene-related proteases are encoded by the human kallikrein gene locus. Clusters of genes exhibit high prostatic or pancreatic expression suggesting evolutionary conservation of elements conferning tissue specificity. These genes are also expressed in a wider range of tissues suggesting a functional involvement of these proteases in diverse physiological processes and perhaps also in pathological events. Inhibition of kallikreins or blockade of kinin receptors offers therapeutic approaches for the prevention or treatment of pathologies. Aprotinin, e.g., has been and is still widely used in open heart surgery resp. extracorporal circulation to reduce blood loss and thus decrease blood transfusion requirement. The C1 esterase inhibitor has been used in the treatment of hereditary angioedema but more recently substituted by a kinin antagonist. The most widespread medical application of a component of the kallikrein-kinin systems has gained inhibitors of kininase II, i.e. the kinin-degrading angiotensin-converting enzyme, the so-called ACE inhibitors, for the treatment of hypertension.