Recent developments in the kallikrein-kinin system with hypertension and diabetes

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Diabetes has been implicated as a major risk factor in the development of cardiovascular and renal complications. Previous studies have indicated altered activities of the bradykinin forming components in diabetic patients as well as diabetic experimental animals. Type 2 diabetes can lead to hypertension, renal and cardiac complications resulting in high rates of mortality worldwide and in Kuwait as well. Bradykinin (BK), a pharmacologically active polypeptide, is one of kinins which is released in the tissues and body fluids as a result of enzymatic action of kallikreins on kininogens. The two types of kallikreins are tissue kallikrein and plasma kallikrein. Tissue kallikrein is mainly expressed in the kidney (urine), glandular tissue, vasculature, heart and brain. It preferentially acts on low molecular weight kininogen substrate to release lysyl-BK. Tissue kallikrein has also been reported to be present in plasma. Plasma kallikrein acts on high molecular weight kininogen substrate to release BK. BK promotes both cardiovascular and renal functions, for example, vasodilation, and diuresis (7,8). BK is rapidly (< 15 sec) inactivated by circulating kinases (9). BK acts on B1 receptors and B2 receptors to elicit physiological and pharmacological actions. It has been shown previously that type-1 diabetic patients are at a risk of developing nephropathy. In addition, BK has been implicated in the pathophysiology of hypertension. In this regard, it is suggested that the role of renal BK is to excrete the excess of sodium. Therefore, a reduction in the generation of renal BK may be the cause in the development of hypertension as a result of the accumulation of sodium in the body. Thus, the development of a compound having renal kallikrein like activity may serve the purpose of excreting excessive sodium from the kidney in the treatment of hypertension. Transgenic mice over expressing renal tissue kallikrein were hypotensive and that administration of aprotinin, a tissue kallikrein inhibitor, restored the BP of the transgenic mice. Recently, it has been proposed that tissue kallikrein gene delivery into various hypertensive models exhibits protection, such as reduction in high blood pressure, attenuation of cardiac hypertrophy, inhibition of renal damage and stenosis. This may indicate the future therapeutics aspect of tissue kallikrein gene therapy for hypertension, cardiovascular and renal pathology. Abnormal BK and nitric oxide levels have been demonstrated in diabetic patients in our study.

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