Angiotensins and Kinins: much more than vasoactive peptides

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The octapeptide Angiotensin II (AngII, the main molecule of the renin-angiotensin system) and kinins, have been classically known as vasoactive peptides, due to their involvement in the modulation of blood pressure, where AngII is hypertensive and kinins act as a hypotensive agent. However, several clinical data point for other functional roles of those peptides, such as participation in cardiovascular and renal diseases, progression of some types of cancer, and also in inflammation. We have recently described that during dental pulp inflammation of rats, an over expression of AT_2 receptor occurs 9 hours after the inflammation induction, in the same period of time that the histopathological analyses revealed increased vasodilation and the infiltration of inflammatory cells. On the other hand, the AT_1 receptor mRNA profile remained constant and unaltered until 24 hours after the inflammation induction, when it presented a drastic reduction of expression (Souza et al., *Regul. Pept.*, 2007). The AT_2 over expression presented a similar profile to that of pro-inflammatory molecules such as the cytokine IL-1β and COX2. We also decided to investigate the possible role of kinins in the central nervous system using a rat model of epilepsy. The modulation of the B_1 and B_2 receptors expression levels in hippocampus of epileptic and control animals was analyzed, and we found that the hippocampal mRNAs for these receptors are significantly up-regulated in a model of temporal lobe epilepsy in the epileptic strain, but not in control animals. We proposed that in this case kinins and their receptors are possibly playing a role in a kininergic neurotransmission pathway, since the usually correlated inflammatory mediators were not up-regulated (Pereira et al., *Int. Immunopharmacol.*, 2008). The major actions of AngII are mediated by activation of the AT_1 receptor. Among kinins, bradykinin (BK) binds to the B_2 receptor and the metabolite des-Arg^9-BK to the B_1 receptor. The AT_1, B_1 and B_2 receptors belong to the G-protein coupled receptor (GPCR) family, and their responses are triggered by activation of Gq protein with subsequent production of inositolphosphates and diacylglycerol as second messengers. In addition to the classical signal transduction pathway, there is increasing evidence that activation of GPCRs also trigger intracellular events primarily attributed only to growth factors receptors. The AT_1 receptor activation leads to phosphorylation of MAPK members, including ERK1 and ERK2, being important to control and coordinate multiple cellular responses such as cellular proliferation and differentiation. We have performed single mutations in the AT_1 receptor aiming at a comparative investigation of activation of distinct signaling pathways. Wild type and mutant-transfected cells were analyzed for their extracellular acidification and calcium mobilization capacities, as well as by ERK1/2 phosphorylation assays. Our results showed that although some of the mutants were not able to induce neither extracellular acidification nor intracellular calcium mobilization, they were fully capable of inducing ERK phosphorylation (Souza et al., *Regul. Pept.*, 2007). These data provided evidence that AT_1 receptor bears different structural features that may be responsible for activation of different signaling pathways, what at least partially, could explain the multiple involvement of this and other GPCRs in different pathophysiological events.

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