PET Imaging of Angiotensin/Endothelin Receptors

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Angiotensin and endothelin are potent vasoconstrictor peptides involved in the systemic and local regulation of tissue perfusion. Endothelin has three isoforms, ET-1, ET-2 and ET-3. There are two physiologically important endothelin receptors: ETAR and ETBR. ETAR is principally found in vascular smooth muscle cells and is involved in vasoconstriction, cellular hypertrophy and cellular proliferation. ETBR is mainly located in endothelial cells of blood vessels and is responsible for the vasodilating effect of endothelin which also entails the release of nitrous oxide. Endothelins and endothelin receptors have been implicated in embryonic and neonatal development, renal homeostasis, cardiac tissue repair after acute ischemia and in regulation of respiration.

In addition to such benefitial effects, endothelins elicit detrimental effects in situations that involve increased vascular tone, chronic tissue damage and remodeling. Radioligands have been developed to image the endothelin receptors such as the selective ligands ^{11}C-PD156707 and ^{18}F-BQV3020 and the nonselective ligands ^{18}F-Endothelin-1 and ^{11}C-L-753,037. ^{11}C-L-753,037 is a mixed ETAR/ETBR antagonist that has been radiolabeled with carbon-11 for PET imaging. In vivo displacement studies demonstrated that in the heart ^{11}C-L-753,037 binds predominantly to ETAR and in the kidneys to both ETAR and ETBR. Imaging studies demonstrated rapid clearance from the circulation and excellent accumulation in the dog myocardium with a high specific binding component. Further basic research studies are being conducted to characterize this radioligand and to synthesize new radioligands suitable for PET.

Angiotensin II is an octapeptide with two membrane targets, AT1R and AT2R. The AT1R receptor is involved in processes such as vasoconstriction of hypertension and arteriosclerosis, hypoxia of renal disease and cardiac hypertrophy of congestive heart failure. The radioligand ^{11}C-L-159,884 has been synthesized and tested excellent for animal studies due to its high renal uptake and specific binding to the AT1R. Animal studies performed with ^{11}C-L-159,884 produced interesting relationships between the RAS (renin angiotensin system) and its target receptor, the AT1R. They demonstrated that increased dietary sodium upregulated AT1R and downregulated the RAS while decreased dietary sodium had the opposite effect. Furthermore, it was found that estrogen depletion upregulated the AT1R receptor but downregulated the RAS while estrogen treatment downregulated the AT1R and upregulated the RAS. In renovascular hypertension both the RAS and the AT1R were upregulated. These preclinical experiments demonstrated not only the ability of PET to study AT1R receptor regulation but also provided interesting insights into the negative feedback mechanisms that control arterial blood pressure and positive feedback mechanisms that may underlie the pathogenesis of arterial hypertension.