0260 : Imidazoline I1 receptor ligands activate hepatic adiponectin pathways and thus improve insulin sensitivity

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Metabolic syndrome is defined as a cluster of cardiovascular and metabolic disorders. Previous studies in rat models of metabolic syndrome have demonstrated that ligands selective for I1 imidazoline receptor (LNPs) increase insulin sensitivity through central sympathoinhibition and an additional peripheral effect attributable to adiponectin, a major insulin-sensitizer adipokine. The objective of this study was to explore possible direct actions on hepatocytes, one of the target cells of insulin and adiponectin.

Experiments were carried out in HepG2 cells, a cell line of hepatocytes. In order to evaluate the effect of LNPs on insulin sensitivity, the activation (i.e. phosphorylation) of a key actor of insulin pathways, AKT, was evaluated by measuring the ratio pAKT/AKT by Western Blot. Similarly, the effect of LNPs on adiponectin signaling was evaluated by measuring the rate of phosphorylation of the central kinase involved in adiponectin pathways, AMPK, by Western Blot. Insulin (10 μM) induced the phosphorylation of AKT (pAKT/AKT=0.49±0.16) compared to control without insulin (pAKT/AKT=0.11±0.03; p≤0.05) whereas LNPs (1μM) alone did not. Interestingly, pretreatment by LNPs (1 μM) during 60 min could potentiate the insulin-induced activation of AKT: LNP509: pAKT/AKT=1.13±0.18 (p≤0.05 vs insulin alone); LNP599: pAKT/AKT=1.23±0.16 (p=0.0545 vs insulin alone).

Concerning adiponectin signaling pathways, LNPs alone (from 10^{-9}M to 10^{-4}M) increased AMPK phosphorylation in a concentration- and time-dependent manner. The maximal effect was obtained after 10 min exposure of LNPs 10 μM (untreated cells: pAMPK/AMPK=0.18±0.04; LNP 509 pAMPK/AMPK=0.38±0.05 p≤0.05; LNP599 pAMPK/AMPK=0.46±0.17). These datasuggest that LNPs on hepatic cells activate adiponectin pathways and potentiate insulin action. These two direct effects on insulin sensitive cells could account for the ameliorated insulin sensitivity observed in vivo.