Angiotensin AT2R Activation Increases ACE2/Ang1-7/MasR Axis and Prevents Fatty-Diet-Induced Obesity

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ABSTRACT

Purpose: Adipose tissue, the obligatory site of fat accumulation causing obesity, expresses local renin angiotensin system (RAS). RAS is commonly known to regulate blood pressure. However recently, we observed that angiotensin type 2 receptor (AT2R) activation prevents high-fat diet (HFD)-induced adiposity and hyperinsulinemia. Although, the mechanism(s) is(are) not known. There is evidence that other RAS components namely, the angiotensin type 1 receptor (AT1R) positively regulates while the angiotensin converting enzyme 2 (ACE2), which catalyzes the production of Mas receptor (MasR) peptide agonist Ang (1-7), inversely regulates adiposity and hyperinsulinemia. In light of the RAS inter-regulatory features, we hypothesize that AT2R activation causes a decrease in AT1R expression and an increase in the ACE2/Ang (1-7)/MasR expression in adipose tissue exerting beneficial effects on HFD-induced adiposity. **Methods:** Male C57BL/6 mice (12-weeks old) were pretreated with AT2R agonist (C21, 0.3 mg/kg, daily i.p.) for 4 days. Thereafter, the animals were placed on normal chow diet (ND) or HFD with concurrent drug treatment for next 10 days. **Results:** The HFD increased the epididymal white adipose tissue (eWAT) weight, plasma free fatty acid (FFA), triglyceride (TG) and insulin levels. The increase in these parameters was prevented by C21 treatment. Western blot analysis demonstrated that HFD increased the protein expressions of AT1R and ACE, but decreased Ang (1-7) peptide level as measured by LC/MS analysis in eWAT. The C21 treatment under HFD condition caused a significant decreased in protein expressions of eWAT AT1R and ACE, but an increase in the expressions of MasR, ACE2 and ANG(1-7) peptide level. **Conclusions**: The pharmacological activation of AT2R with C21 affects adipose RAS components i.e., an increase in ACE2/Ang(1-7)/MasR levels and a decrease in ACE/AT1R expression, improving lipid metabolism and hyperinsulinemia under HFD

condition. We propose that the pharmacological activation of AT2R may serve as therapeutic target for controlling obesity and associated metabolic disorders.

KEY WORDS: Angiotensin Receptors, Angiotensin Converting Enzyme 2, Obesity