Letter to the editor

Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker for the prevention of type 2 diabetes mellitus?

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Dear Editor

Previous large-scale clinical studies showed that the incidence of the new onset of diabetes as a secondary endpoint was lower in patients treated with either angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) than those individuals treated with other kinds of anti-hypertensive drugs or placebo [1]. These promising observations especially HOPE trial (ramipril vs placebo, 30% reduction in the new onset of diabetes, $p < 0.001$ in the *post hoc* analysis) led to the initiation of ramipril to prevent the development of diabetes as a primary endpoint in subjects with impaired fasting glucose [2]. However, the ramipril trial failed to reduce the incidence of diabetes at the end of the study [2]. In contrast, a recent prospective, large-scale, double-blind, placebo controlled study reported that valsartan significantly lowers the incidence of new-onset of diabetes in subjects with impaired glucose tolerance[3]. Why ramipril can not reduce the incidence of diabetes as valsartan is currently unknown. Here, we report the different effect on the activation of PPARγ between ACEI and ARB, which may offer part of the speculations for the selection between these two drugs to prevent the development of diabetes in patients with hypertension and impaired fasting glucose or impaired glucose tolerance. The detailed description of the methods for measurement of PPARγ activation and glucose uptake was reported in our previous study [4]. In brief, for the measurement of PPARγ

activation, HuH-7 cells were transiently transfected with 0.5 μg of PPREγ reporter constructs and 0.1 μg of cytomegalovirus-β-galactosidase vector (pCMV-β-Gal). After transfection, HuH-7cells were incubated in the presence of solvent alone (served as control) or varying doses of ACEI or ARB for 24 hrs. A 2 μM rosiglitazone was used as a positive control. The luciferase activity of PPREγ reporter plasmid-transfected cells divided by the β-galactosidase activity of pCMV-β-Gal-transfected cells represents the relative PPARγ activation of each experiment. As shown in figure, losartan and irbesartan instead of ramipril and imidapril significantly elevated PPARγ activation in various doses in HuH-7cells. We further used 2-deoxy-D-[^{3}H] glucose to evaluate the glucose uptake effect of irbesartan. We found that comparing with the control group, irbesartan at concentrations of 8 μM (546.1±70.7 dpm vs 476.9 ± 257.9 dpm, $p < 0.05$) and 10 μM (725.9±367.7 dpm vs 476.9 ± 257.9 dpm, $p < 0.05$) significantly increased the level of glucose uptake in 3T3-L1 cells. In conclusion, ARB increased PPARγ activation and stimulated glucose uptake. Lack of the effect on the PPARγ activation in ACEI may explain part of the mechanisms of the negative result of the ramipril study.

Key words: Angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, DM

Conflict of interest

Dr Ching-Chu Chen has received lecture fee from MSD, Sanofi Aventis, Novatis and has been reimbursed by Sanofi Aventis for attending international diabetes conference. These companies manufacture ARB for the treatment of hypertension.

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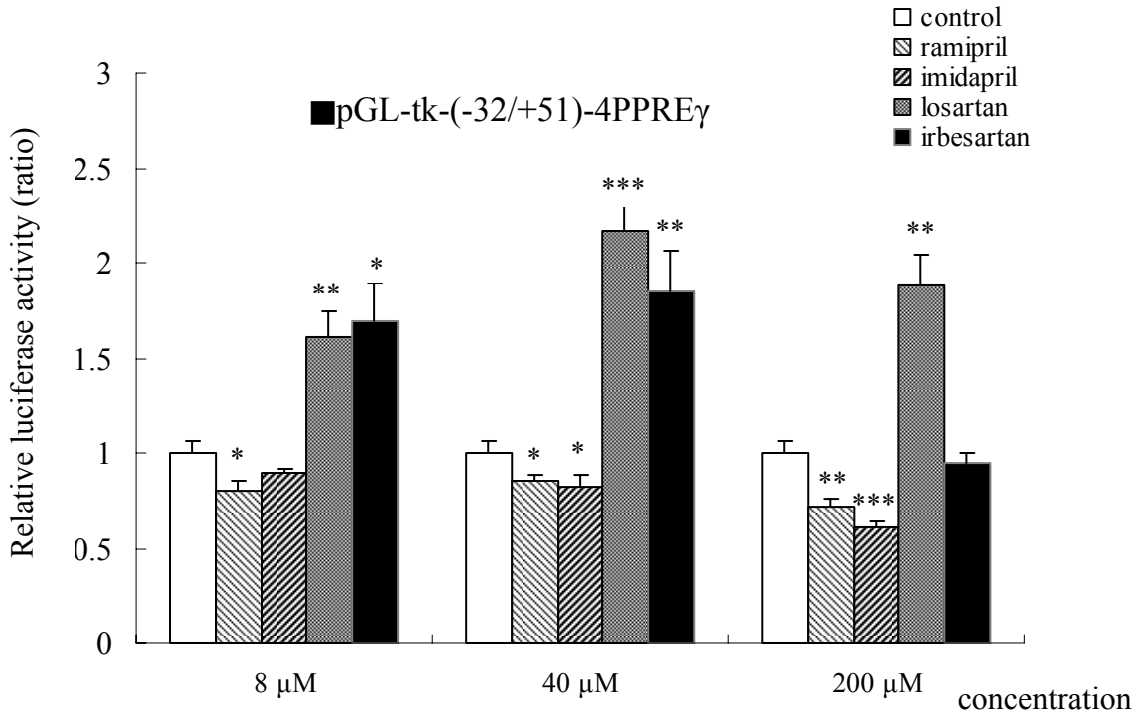

Figure. Activation of PPREγ reporter gene (pGL-*tk*-(-32/+51)-4PPREγ) activity by angiotensin II receptor blocker (losartan and irbesartan) but not angiotensin converting enzyme inhibitor (ramipril and imidapril) in HuH-7 cells. The PPARγ activation of ACEI and ARB was presented as the relative activity of the control group. *p < 0.05, **p < 0.01, ***p < 0.005.