Topic 25 – Hypertension: Pharmacology – B

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0428

Binding mechanism of pharmacological inhibitors and antihypertensive food peptides to human somatic angiotensin I-converting enzyme (ACE)

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Angiotensin I-converting enzyme (ACE), which is a key enzyme of the renin-angiotensin system, is one of target for antihypertensive molecules. Indeed, ACE is well known for its involvement in hypertension which is the main risk factor involved in the development of cardiovascular and kidney diseases and is a major cause of morbidity and mortality. Currently, many pharmacological ACE inhibitors (captopril, lisinopril…) are used for hypertension treatment, but their administration over a long period is associated with some undesirable side effects. Furthermore, there are many publications dealing with antihypertensive peptides from food proteins. ACE-inhibitory peptides, generated by hydrolysis of food proteins, may be a natural alternative to prevent hypertension appearance. However, among the bioactive peptides published in the literature as ACE inhibitors, a very small number really displays an antihypertensive activity *in vivo* in animals. Moreover, their mechanism of action at the molecular level is still misunderstood. The objective of our work was to characterize the molecular interactions between ACE and some peptides described as ACE-inhibitors, which have or not a true antihypertensive activity *in vivo*. For this purpose, a methodology already developed in our teams was employed (Zidane *et al*., 2013). It is based on the use, for the first time, of Biacore® technology (SPR). This real time technology provides some important molecular information such as the rate constants of association and dissociation, the stoichiometry and the site of the interaction on ACE. In our study, the direct interaction between ACE and inhibitors (without substrate or ligand) showed dissociation constants (K_D) of the same order of magnitude as IC_{50}. Moreover, the formed ACE-inhibitor complexes are unstable. Given these results, it is difficult to attribute significant antihypertensive effect demonstrated *in vivo* for these peptides (for example IPP, VPP) to the only ACE inhibition.

0272

True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence

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Objective: We previously showed (Bobrie et al. J Hypertens 2012) that sequential-nephron blockade (SNB) was more effective than combined renin angiotensin system blockade (RB) for controlling BP in patients with resistant hypertension (RH). In this post-hoc analysis, we assessed medication adherence (MA) and its influence on the antihypertensive response to SNB/RB with a new combined scoring system.

Design and Method: Pts with daytime ambulatory SBP/DBP (dASBP/dADBP) >135 and/or 85 mmHg, despite 4 week-treatment with irbesartan 300 mg+HCTZ 12.5 mg+amlodipine 5 mg, were randomised either to SNB (i.e.+spironolactone 25 mg, then +furosemide 20-40 mg, then +amiloride 5 mg, n=82) or RB (ramipril 5-10 mg, then bisoprolol 5-10 mg, RB group, n=82) for 12 weeks. MA was scored according to 4 criteria: (i) trough/peak plasma irbesartan (Irb) concentration (HPLC); (ii) urinary AcSDKP/creatinine

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ratio (UR) to evaluate ramipril intake; (iii) delay of last medication intake before visit (LMI); and (iv) pill counting (PC, %). One point of MA score was attributed to trough Irb >20ng/ml, UR >4nmol/mmol, LMI <24h and PC >80%. MA was defined as low (LMA, score <2), intermediate (IMA, score=3), and optimal (OMA, score=4).

Results: 82 pts among 164 had OMA (46 SNB and 36 RB); 52 pts had IMA (23 SNB and 29 RB); and 30 pts had LMA (13 SNB and 17 RB) (inter-groups difference: NS). LMA pts were younger than SMA pts (50±11 vs. 56±10 yrs, p<0.011). In OMA pts, the difference in dASBP/dADBP between SNB vs RB was significant (–11 [–17;–6]/–6 [–9;–2] mmHg, p<0.0001/p=0.0025), favoring SNB, whereas in LMA pts the significant difference between the two groups was no more observed (–6 [–19;7]/–1 [–10;7] mmHg, p=0.352/p=0.7096).

Conclusion: The major BP lowering effect of SNB vs. RB observed in pts with OMA is lost in pts LMA. Combined methods for assessing MA allow determining the true efficacy of antihypertensive strategies in patients with RH. Reinforcement of MA in RH pts is deemed necessary.

0273

Beneficial effect of sequential nephron blockade on central pressure and large artery remodeling in resistant hypertension

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Objective: We have previously shown that combined renin-angiotensin system blockade (RB) was less effective than sequential-nephron blockade (SNB) for controlling BP in resistant hypertension (RH). Whether this is accompanied with an improvement in the mechanical properties of large arteries is unknown.

Design and Method: Pts with daytime ambulatory SBP/DBP (dASBP/dADBP) >135 and/or 85 mmHg, despite 4 week with irbesartan (Irb)+HCTZ+amlodipine, were randomised to SNB (n=82) or RB (n=82) for 12 weeks. Central pulse pressure (CPP) and carotid-femoral pulse wave velocity (PWV) were measured by aplanation tonometry. High-resolution echotracking system (Walltrack®) was used to measure carotid artery diameter (Dcca), wall thickness (WT), circumferential wall stress (CWS), and stiffness. All parameters were measured at baseline and week 12.

Results: Baseline clinical characteristics did not differ between groups. dASBP decreased more in SNB (–19±12 mmHg) vs RB (–8±13 mmHg, p<10-6), either for CPP [SNB (–12.8±16.9 mmHg) vs RB (–1.0±9.3 mmHg, p<0.006)] after adjustment on baseline CPP and deltaMeanBP. CCA stiffness and PWV decreased similarly in both groups. Dcca decreased more in SNB (–267±46 μm) vs RB (–7.8±39 μm, p=0.01) after adjustment on baseline D and deltaASBP. WT did not differ and CWS decreased more in SNB (–15.2±16.5 kPa) vs RB (–5.2±12.6 kPa, P=0.001).

Conclusions: In RH pts, a ttt strategy based on SNB improved CPP to a greater extent than a RB strategy. This may lead to a better target organ damage prevention and CV outcome. SNB improved CWS. Whether this effect is due aldosterone blockade or sodium depletion remains to be investigated.

0063

Effect of nebivolol treatment during pregnancy on the genital circulation, fetal and postnatal development in the wistar rat

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Introduction: This study was designed to evaluate the effect of nebivolol (vs. bisoprolol) on the genital circulation, fetal growth and postnatal development in wistar rat.

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