

## NEPRILYSIN INHIBITION AS A NEW ANXIOLYTIC TARGET IN MAN – NO MECHANISM VIA CYCLIC GUANOSINE MONOPHOSPHATE?

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received: 6. 2. 2024;

revised: 14. 2. 2024;

accepted: 29. 2. 2024

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### Dear Editor,

A new potential for anxiety treatment is discussed for several cardiovascular therapeutics according to a current review of preclinical and clinical data (Repova et al. 2022). We have provided first evidence for an acute anxiolytic effect of the cardiologically established neprilysin inhibitor and angiotensin receptor blocker sacubitril/valsartan (S/V) in patients suffering from heart failure with reduced ejection fraction (HFrEF), in whom anxiety is a frequent symptom, after one week of treatment in a small, observational pragmatic trial including a control group (Kellner et al. 2023). This acute anxiolysis persisted when statistically controlling for amelioration of heart failure under S/V treatment. Our a priori hypothesis of the underlying mechanism was that neprilysin inhibition by S/V increased plasma atrial natriuretic peptide (ANP), which has an acute anxiolytic-like effect in man (Wiedemann et al. 2001). However, plasma ANP was not significantly elevated after one week of S/V in our study. Kobalava et al. (2016) used plasma levels of cyclic guanosine monophosphate (cGMP), which is produced by activation of guanyl cyclase-coupled receptors by ANP, as a marker of neprilysin inhibition. They showed a significant increase of cGMP after one week of S/V treatment in HFrEF patients, but – in accordance to our data – not for plasma ANP. However, ANP is a difficult analyte due to rapid degradation and complicated measurement. Now we determined cGMP in plasma samples from our above cited study, hypothesized its significant increase by one week of S/V treatment and further investigated the relationship of cGMP changes with the anxiolytic effects of S/V.

In 35 patients suffering from decompensated HFrEF – 23 on S/V (24 mg/26mg b.i.d., 19 men, 4 women, age  $66.1 \pm 2.7$  years, left ventricular ejection fraction (LVEF)  $29.6 \pm 1.2$  %) and 12 receiving treatment as usual (TAU) without S/V (7 men, 5 women, age  $66.3 \pm 4.3$  years, LVEF  $30.6 \pm 1.6$  %) – venous blood was obtained after 15 min in supine on days 0 and 7. cGMP in plasma was measured by a commercial radioimmunoassay (IBL International GmbH, Hamburg, Germany); inter- and intra-assay coefficients of variation were below 12%. Further methodological aspects and clinical details were already

published (Kellner et al. 2023). There, the results of the anxiety ratings, using the validated Hospital Anxiety and Depression Scale (HADS), had already been reported. The protocol had been approved by the ethics committee of the Ruhr University Bochum and all subjects had given written informed consent prior to participation. This trial was recorded in the WHO recognized German Register for Clinical Studies (DRKS#00012906).

cGMP increased in plasma from  $11.8 \pm 1.7$  pmol/ml (mean  $\pm$  SEM,  $n=22$ ) at baseline to  $16.7 \pm 3.1$  pmol/ml after one week of S/V treatment, while no rise was seen under TAU ( $n=12$ ):  $15.5 \pm 2.7$  to  $15.0 \pm 2.8$  pmol/ml. (An outlier from the S/V group rising from 34.5 to 43.5 pmol/ml had been removed before statistical analysis.) Applying an analysis of covariance on the differences of the cGMP plasma values after and before treatment with baseline cGMP as a covariate, we found a significant treatment effect ( $F(1,32)=4.845$ ,  $p=0.035$ ). This treatment effect is attributable to the strong increase in cGMP after one week of S/V use compared to baseline. The previously reported anxiolytic effect of S/V on HADS-anxiety ratings was demonstrated in the experimental group when performing an analysis of covariance with cGMP as a covariate: Anxiety declined significantly within one week from  $6.5 \pm 0.9$  to  $4.6 \pm 0.6$  (time effect  $F(1,21)=9.52$ ,  $p=0.006$ ), whereas the covariate cGMP did not have a significant effect ( $F(2,19)=1.29$ ,  $p=0.297$ ). Interestingly, also for the ratios of the day 7/day 0 measurements of plasma cGMP and respective HADS-anxiety ratings under S/V no significant correlation was detected (Spearman correlation coefficient  $r=0.197$ ,  $p=0.391$ ).

The observed significant increase of plasma cGMP indicates inhibition of neprilysin by S/V in accordance with a previous study administering double the dose of S/V (Kobalava et al. 2016). However, we did not observe an association of plasma cGMP increases and the acute anxiolysis under S/V. This finding raises doubts concerning the hypothesized role of ANP as a mediator of this anxiolytic effect. Observed baseline differences of cGMP between our groups remain unexplained. Replication of the so far preliminary clinical data about anxiolysis by neprilysin inhibitor S/V in heart failure is necessary in large and

well-controlled prospective randomized double-blind studies, with different dosages of S/V, using valsartan as comparison condition, particularly in patients with high anxiety scores. Such studies should also be performed in patients with primary anxiety disorders. Because neprilysin is a “promiscuous enzyme” with a large variety of potential substrates (Singh et al. 2017), underlying anxiety modulating mechanisms of neprilysin inhibition via behaviorally active peptides beyond ANP (such as enkephalin, substance P, adrenomedullin, neuropeptide Y, etc.) need future research. Neprilysin inhibition remains an interesting target for potential anxiety modulation in man.

**Acknowledgments:** The authors would like to thank Mrs. Iris Remmlinger-Marten and Mrs. Kirsten Dammann (Dept. of Psychiatry and Psychotherapy, University Hospital Hamburg-Eppendorf) for expert technical assistance.

**Ethical Considerations:** Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

**Conflict of interest:** No conflict of interest

**Funding sources:** The authors received no funding from an external source.

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## EFFICACY OF TRANSCUTANEOUS AURICULAR VAGAL NERVE STIMULATION AND JACOBSON RELAXATION TECHNIQUE ON STRESS MANAGEMENT AMONG HEALTH SCIENCE CRRI POPULATION

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received: 18. 1. 2024;

revised: 4. 2. 2024;

accepted: 11. 2. 2024

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Dear Editor,

We would like to share our experience with the Psychiatric Danubina audience that stress is a major mental health issue. The word ‘stress’ is the consequence of an individual’s physical, mental and emotional strain (Salam et al. 2013). In this modern world, people are under a lot of pressure, but workplace stress has taken on a special significance (Franza et al. 2015). Stress in the workplace results in physical and psychological reactions that increase the chance of adverse health effects (Öğütü et al. 2021).

Emotional and physical wellbeing are closely linked to the ability to work efficiently (Franza F et al. 2015). Stress is more common in health profession than in other field (Grace & VanHeuvelen 2019). Healthcare professionals work involves them interacting with their emotional feelings of sufferings, empathy and exhaustion (Franza et al. 2015). It is unknown to health science students that how stress can cause illness, health changes, unsatisfactory in the patient care and inattention (Periasamy et al. 2023).

Studies has shown that non-invasive transcutaneous vagal nerve stimulation (TaVNS) (Wu et al. 2022) and Jacobson