

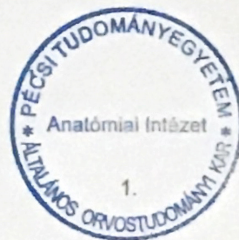
CHANGES OF BLOOD PACAP LEVEL IN PATIENTS WITH PARKINSON'S DISEASE

01/29/2020

Daniel Pham¹, Balazs Daniel Fulop¹, Beata Polgar², Zalan Szanto³, Adel Jungling¹, Norbert Kovacs⁴, Istvan Balas⁵, Endre Pal⁴, Tunde Toth¹, Balazs Fazekas¹, Robert Herczeg⁶, Attila Gyenesei⁶, Dora Reglodi¹, Andrea Tamas¹

¹Department of Anatomy, MTA-PTE PACAP Research Team, Centre for Neuroscience, ²Department of Medical Microbiology and Immunology, ³Department of Surgery, ⁴Department of Neurology, ⁵Department of Neurosurgery, ⁶Szentagothai Research Center, Medical School, University of Pecs, Pecs, Hungary

In the last few years, numerous studies examined changes of PACAP level in human samples to show alterations in various physiological and pathological conditions. There were several studies in the field of neurology as well. Significantly increased plasma PACAP concentrations were present after acute spontaneous basal ganglia hemorrhage, reduced levels in Alzheimer's disease patients in several brain areas and in the cerebrospinal fluid. We found correlation between mortality and PACAP levels in severe traumatic brain injury. Our aim was to examine the PACAP in blood samples of patients with Parkinson's disease (PD), (n=107, control=39). We measured plasma PACAP38 level of PD patients and searched for correlations with clinical properties such as gender, age, stage and subtype of disease, type of treatment and specified scores for PD. Sandwich-type ELISA (Mybiosource) was used to measure the PACAP38 level of plasma samples. We showed significantly decreased PACAP38 levels in PD patients over 50 years and in Hoehn-Yahr scale stage 3 but elevated PACAP38 levels was found after deep brain stimulation. We didn't find significant correlations between plasma PACAP38 levels and MDS-UPDRS or the type of pharmacological treatment. Our results are similar to earlier experiments where elevated PACAP38 levels were found after basal ganglia or subarachnoid hemorrhage, traumatic brain injury, in migraine and post-traumatic stress disorder. The neuroprotective and cytoprotective effects of PACAP are well known therefore it suggests the possibility of using PACAP as a biomarker to monitor the course of the disease and foretell the prognosis of this neurodegenerative disorder.



CHANGES OF BLOOD PACAP LEVEL IN PATIENTS WITH PARKINSON'S DISEASE

Daniel Pham¹, Balfazs Daniel Fulop¹, Beata Polgar², Zalan Szanto³, Adel Jungling¹, Norbert Kovacs⁴, Istvan Balas⁵, Endre Pal⁴, Tunde Toth¹, Balazs Fazekas¹, Robert Herczeg⁶, Attila Gyenesi⁶, Dora Reglodi¹, Andrea Tamas¹

¹Department of Anatomy, MTA-PTE PACAP Research Team, Centre for Neuroscience, ²Department of Medical Microbiology and Immunology, ³Department of Surgery, ⁴Department of Neurology, ⁵Department of Neurosurgery, ⁶Szentagothai Research Center, Medical School, University of Pecs, Pecs, Hungary

Introduction

- Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide with several antiapoptotic, antioxidant, regulatory and antiinflammatory effects proved by numerous *in vitro* and *in vivo* studies.
- In the last few years, several studies examined changes of PACAP level in human samples to show alterations in various physiological and pathological conditions including the following in the field of neurology:
 - Significantly increased plasma PACAP concentrations were present after acute spontaneous basal ganglia or subarachnoidal hemorrhage, traumatic brain injury and also in migraine.
 - Reduced PACAP levels were found in Alzheimer's disease patients in several brain areas and in the cerebrospinal fluid (CSF).
 - Reduced PACAP levels were found in multiple sclerosis in the CSF.
 - Earlier experiments did not show significant changes of PACAP levels in CSF in the case of patients with Parkinson's disease (PD).
- We proved in several PD animal models the neuroprotective effect of PACAP on dopaminergic cells that suggests its important role in the pathomechanism of this disease.
- Based on these results our aim was to examine PACAP in plasma samples of patients with Parkinson's disease.

Results

We showed:

- significantly decreased PACAP-38 levels in non-DBS patients compared to healthy controls (Fig.2)
- significantly elevated PACAP-38 levels in DBS treated patients compared to non-DBS patients (Fig.2)
- significantly decreased PACAP-38 levels in HYS3 compared to HYS2 patients (Fig.3)
- significantly decreased PACAP-38 levels in PD patients over 50 years compared to patients younger than 50 years (Fig.4)
- no significant correlation between plasma PACAP-38 levels and MDS-UPDRS or the type of pharmacological treatment (Fig.5)

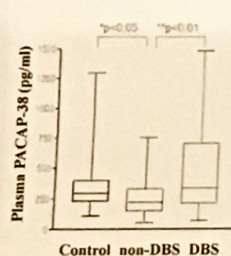


Figure. 2 PACAP-38 levels in healthy population (control), non-DBS and DBS-treated PD patients

Significantly lower PACAP-38 levels were present ($p=0.05$) in the plasma samples of non-DBS treated PD patients in comparison to healthy control individuals.

In DBS treated patients PACAP-38 levels were significantly elevated ($p=0.01$) in the plasma of PD individuals when compared to non-DBS treated patients.

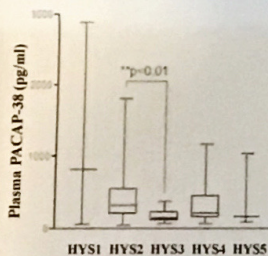


Figure. 3 PACAP-38 levels in different stages of PD

Five subgroups were made according to the HYS: HYS1 ($n=4$), HYS2 ($n=60$), HYS3 ($n=16$), HYS4 ($n=19$) HYS5 ($n=3$).

The analysis revealed a progression-dependent negative correlation between plasma PACAP-38 levels and the stages of PD. PACAP-38 levels decreased firmly until HYS3, thereafter remained steady.

The differences were significant ($p=0.01$) between the HYS2 and HYS3 stages.

Methods

We measured plasma PACAP-38 level of PD patients and searched for correlations with clinical properties such as gender, age, stage and subtype of disease [based on the Hoehn and Yahr scale (HYS), Fig.1], type of treatment [pharmacological or deep brain stimulation (DBS)] and specified scores for PD [e.g. Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), evaluating non-motor and motor experiences of daily living and motor complications].

Sandwich-type ELISA (Mybiosource) was used to measure the PACAP-38 level of plasma samples (PD patients=107, control=39).

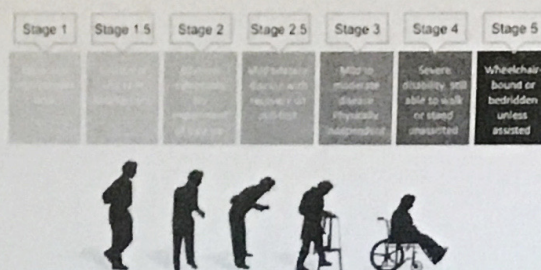


Figure. 1 HYS is a commonly used scale for measuring the severity of PD symptoms, classifies patients in five stages. <http://gopezzi.info/similar/5-stages-of-parkinsons-headline.html>

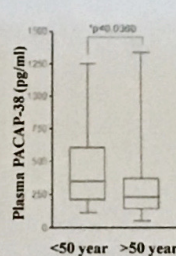


Figure. 4 Age-dependent differences of PACAP-38 levels in PD

Plasma concentration of PACAP-38 was significantly lower ($p=0.0360$) when the age at diagnosis of PD was more than 50 years in comparison to the younger (age <50 years) group.

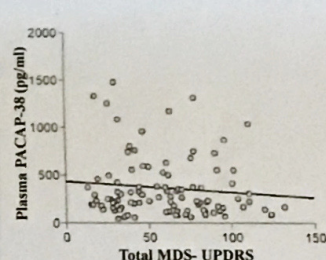


Figure. 5 PACAP-38 levels and total points of MDS-UPDRS

Comparing ELISA results with the MDS-UPDRS score did not reveal significant correlation between plasma PACAP-38 levels and total MDS-UPDRS scores but showed a weak negative tendency.

Conclusion

- Earlier experiments did not find significant changes in CSF PACAP levels of PD patients, however, our experiments showed **decreased level** in plasma samples. The lowest PACAP levels were measured in HYS3 and in older ages.
- The reduced levels of PACAP found in PD patients and the significant **increase** after DBS treatment confirm the hypothesis that the neuroprotective effect of PACAP could have a role in this disease. The exact origin of increased PACAP levels in DBS treated patients is yet unknown, we propose further examinations to reveal the exact pathomechanism.
- Based on our results we suppose the possibility of using PACAP as a **biomarker** to monitor the course of the disease and foretell the prognosis of this neurodegenerative disorder.

Acknowledgements

Support: K119759, K115874; GINOP-2.3.2-15-2016-00050 "PEPSYS", EFOP-3.6.3-VEKOP-16-15 2017-00008, Hungarian Brain Research Program 2017-12.1-NKP-2017-00002, EFOP-3.6.2-16-2017-00008, University of Pecs Medical School KA Research Grant KA-2019-30, TAMOP-4.2.4.A/2-11-1-2012-0001; New Hungarian National Excellence Program UNKP-16-4-IV UNKP-2018-4, Hungarian Academy of Sciences MTA-TKI-14016, 20765-3/2018/FEKUTSTRAT, 2019 Fikp II, EFOP-3.6.1-16-2016-000004, Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences.