Altered kynurenine pathway in episodic migraine patients: potential peripheral biomarkers during the interictal period

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INTRODUCTION

Altered glutamatergic neurotransmission play a central role in migraine patomechanism. The kynurenine pathway (KP) is closely related to the glutamatergic system. Since the inhibition of N-methyl-D-aspartate (NMDA) receptors is believed to protect against glutamate-caused excitotoxicity, and kynurenic acid (KYNA) – which is one of the metabolite in the KP – has a competitive antagonist effect on these receptors, it is possible that the KP has therapeutic potential in headache disorders.

AIMS

1. To determine the concentrations of main metabolites of tryptophan (Trp) pathway in the peripheral plasma of episodic migraine patients compared to healthy subjects.
2. To distinguish between metabolic alterations in the interictal/ictal periods and in the two subgroups of patients (migraine with and without aura).
3. To describe the relationship between altered Trp metabolism and clinical features of the disease/attacks.

METHODS

- Inclusion criteria: Female episodic migraine (EM) patients fulfilling the criteria of the 3rd edition of The International Classification of Headache Disorders were registered, aged between 25-50 years (n=50) and healthy control subjects (n=34) were recruited.
- Exclusion criteria: both the EM and control group included the presence of other type of headache (e.g tension type headache) less than 48 hours before sampling, or serious systemic disorders, or other chronic pain condition and depression.

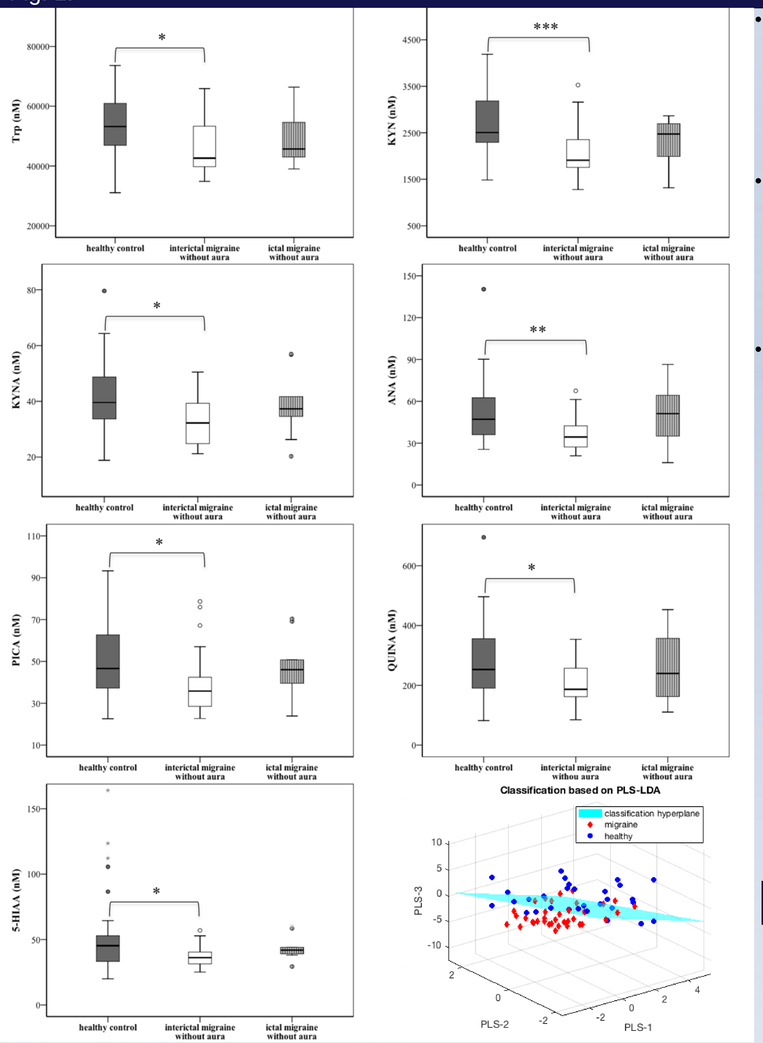
Blood samples were collected from cubital veins of patienst during the inetrictal (attack free) (n=47) and ictal (attack) (n=12) periods and from healthy controls on one occasion. 12 metabolites of TRP pathway were determined by neurochemical measurements (ultra high performance liquid chromatography-tandem mass spectometry (UHPLC-MS/MS.)

REFERENCES

Tuka et al. Clinical relevance of depressed kynurenine pathway in episodic migraine patients: potential prognostic markers in the peripheral plasma during the interictal period. J Headache Pain. 2021 Jun 25;22(1):60.

RESULTS

Fig. 1.



*Differences in plasma levels of Trp, KYN, KYNA, ANA, PICA, QUINA and 5-HIAA between groups of interictal/ictal phases of migraine without aura patients and healthy subjects. Significance levels: * p < 0.05, ** p < 0.01, *** p < 0.001.*

3D-projection plots of migraine and healthy metabolite profiles in the PLS latent variable space. The classification hyperplane was obtained using linear discriminant analysis.

- Plasma concentrations of the most Trp metabolites were remarkably decreased in the interictal period of migraineurs compared to healthy controls, especially in the migraine without aura (MWoA) subgroup (Fig. 1).
- Several metabolites showed tendency to elevate during the ictal phase (Fig. 1 and 2.) and higher interictal KYNA levels were identified in patients whose headache was severe and not related to their menstruation cycle.
- Negative linear correlation was detected between the interictal levels of xanthurenic acid and attack frequency, while positive associations were found between the ictal 3-hydroxykynurenine levels and the beginning of attacks; and the ictal picolininc acid levels and the last attack before ictal sampling.

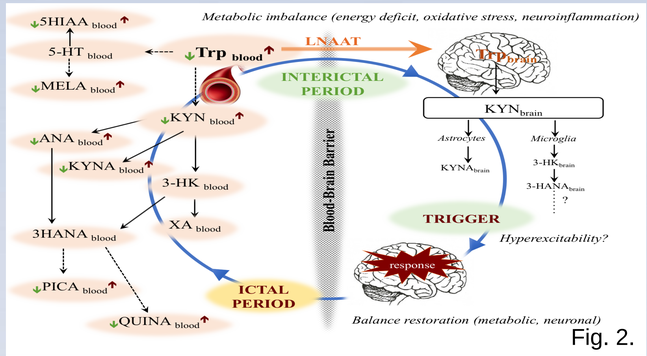


Fig. 2.

CONCLUSIONS

Our results show that the entire metabolic route is significantly depressed during the interictal period in migraineurs, which might act as trigger for the next attack. The headache (hyperexcitability) might be a response to glutamate excess or oxidative stress. Supposedly, in the CNS of migraineurs the brain is able to take up Trp from the periphery, to protect the brain from damage (counterbalancing excitotoxicity) (Fig. 2).