A Role of Astrocytic Glutamate Regulation in Interferon-α-Induced Depression: Supporting Evidence from Genetic Association Studies

Szu-Wei Cheng[1,2], Daniel Tzu-Li Chen[2,3,4], Jane Pei-Chen Chang[1,2], Kuan-Pin Su[1,2,3,5]

[1]College of Medicine, China Medical University, Taichung, Taiwan; [2]Department of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan;
[3]Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan; [4]School of Chinese Medicine, China Medical University, Taichung, Taiwan;
[5]An-Nan Hospital, China Medical University, Tainan, Taiwan

ABSTRACT

Background: Depressives episodes occur in up to one-third of patients treated with interferon-α (IFN-α-induced depression), which is strong supportive evidence for the inflammation theory of depression. As the pathogenic role of a dysregulated glutamatergic system has been highlighted in the recent years, investigating genes related to astrocytic regulation of glutamate may shed some insights on this disease. The aim of the study is to identify the at-risk genetic variations related to astrocytic glutamate regulation in IFN-α-induced depression.

Method: In this prospective case-control study, we assessed 291 patients with chronic hepatitis C viral infection treated with IFN-α. Genomic DNA from peripheral blood samples was sequenced by Affymetrix TWB array. Single nucleotide polymorphisms (SNPs) in genes related to astrocytic regulation of glutamate were analyzed with allelic association tests by Plink. Family-wise error rates were controlled with 5000 gene-wide permutations. For significant SNPs, stratified analyses were conducted to control for confounders and adjust odds ratios if needed.

Results: rs972354 in *BEST1* (empirical p-value=0.0280), rs9421574 (empirical *p*-value=0.0170), rs17343630 (empirical *p*-value=0.0364), and rs9421579 (empirical *p*-value=0.0152) in *GLUD1* were significantly associated with IFN-α-induced depression. Stratified analyses showed no signs of confounders.

Conclusion: This study supports the involvement of astrocytic glutamate regulation in IFN-α-induced depression.

Introduction

- One-third of patients develop major depression during IFN-α therapy (IFN-α-induced depression).
- Recent studies revealed glutamate-related genetic predisposition for IFN-α-induced depression, implying the importance of a dysregulated glutamatergic system in the pathogenesis of this disease.
  - Genetic variations in ionotropic glutamate receptor pathways were found associated with IFN-α-induced depression (Cheng et al 2021)
  - Genetic variations in the kynurenine pathway were also found associated with IFN-α-induced depression (Cheng et al 2021). As the pathway can be affected by IFN-α and produce quinolinic acid, a neurotoxin which induces glutamate excitotoxicity, it may be the upstream pathogenic pathway.
- Astrocytic glutamate regulation may also play a role in IFN-α-induced depression.

Method

- A total of 291 hepatitis-C-virus infected patients were treated with IFN-α and assessed the occurrence of IFN-α-induced depression in the course of 24 weeks. Sociodemographic factors (marital status, education level, sex and age) were also recorded.
- Genomic DNA was extracted from leukocytes and genotyped with Affymetrix TWB array.
- After quality control procedures, we employed allelic association tests with 5000 gene-wide permutations to test 23 candidate genes related to astrocytic glutamate regulation.
- Stratified analyses were conducted to control for confounders for significant single nucleotide polymorphisms (SNPs).

Results

- There were 66 cases and 225 controls with significantly different sex ratio (p = 0.003) and education levels (p = 0.030).
- As shown below, SNPs in *BEST1* and *GLUD1* were significantly associated with IFN-α-induced depression.
- Stratified analyses showed no signs of confounders.

Table 1. Significant SNPs

Gene	SNP	Empirical *P*-value	*P*-value	Minor Allele	Major Allele	OR
BEST1	rs972354	0.0280	0.0122	C	T	0.5569
GLUD1	rs9421574	0.0170	0.0062	C	T	1.7260
	rs17343630	0.0364	0.0106	T	C	2.3800
	rs9421579	0.0152	0.0046	C	T	1.7600

Abbreviations: OR: odds ratio; SNP: single nucleotide polymorphism
Empirical *p*-value means the *p*-values obtained with permutations.
P-value means the *p*-values obtained in the original $\chi 2$ tests.
OR means the odds ratio for minor allele with major allele as reference.

Conclusion

- Best1 channels are mostly found in peri-synaptic astrocytes, and mediate the glutamate release (Woo et al 2012), whereas *GLUD1* encodes glutamate dehydrogenase, which is abundant in the brain and catalyses the oxidative deamination of glutamate.
- As both significant genes are important in astrocytic glutamate regulation, this study supports its involvement in IFN-α-induced depression.