LEPTIN SIGNALLING GENETIC VARIANTS AND INSULIN RESISTANCE IN MULTIPLE SCLEROSIS PATIENTS

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INTRODUCTION

Last decade provided multiple evidence that link disturbances in metabolic processes and energy metabolism with diseases of central nervous system and neurodegeneration. Initial phases of insulin resistance (IR) are present in natural course of multiple sclerosis (MS) and leptin (LEP) was recognized as a player in MS pathophysiology and moreover cognitive decline.

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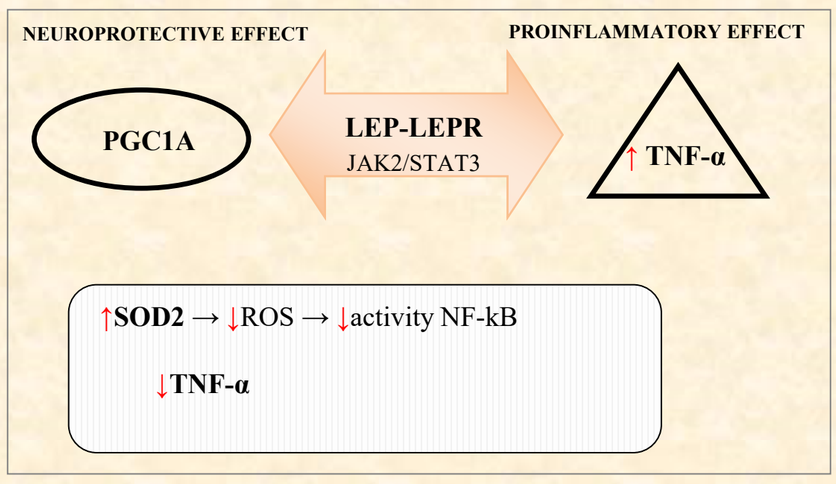


Figure 1. LEP singnaling in MS pathogenesis: possible proinflammatory and neuroprotective effects

We aimed to investigate association of genetic variants in LEP rs7799039, its receptor LEPR rs1137101 and proliferator-activated receptor gamma co-activator 1-alpha (PGC1A) rs8192678 with IR parameters (HOMA-IR index, area under the curve for insulin and glucose, Cederholm insulin sensitivity index (ISIced), the insulinogenic index in the first 30 min of oral glucose tolerance test (OGTT) in patients with MS.

METHODS

This study included a **78 relapsing-remitting (RRMS) patients (age** (mean±SD)= **37.1±9.7 yrs.; 38 women and 40 men, mean EDSS=2.5**) in clinical remission, free of corticosteroids for at least three months. The glucose tolerance, insulin resistance (IR) and reduced insulin sensitivity (IS) were examined using an oral glucose tolerance test (OGTT) and using basal plasma glucose and insulin levels. HOMA-IR index, the value obtained from the product of basal insulin levels (I0, mU/mL) and basal glycemia (G0, mmol/L) divided by the constant 22.5 (IR considered if HOMA-IR ≥ 2.5). Cederholm index (ISIced) is a measure of peripheral insulin sensitivity.

Genotyping was performed using TaqMan® technology. Statistical analysis was performed using Statistica Version 8, software package (StatSoft Inc, 2008). In all tests, the differences with two-tailed alpha–probability $p < 0.05$ were considered significant.

RESULTS

None of the 3 variants' genotypes were associated with HOMA-IR index , area under the curve for insulin and glucose and the insulinogenic index.

Leptin gene variant was significantly associated with IGT (Table 1.). PGC1A variant was significantly associated with ISIced (Figure 2.). None of the variant showed association with IR.

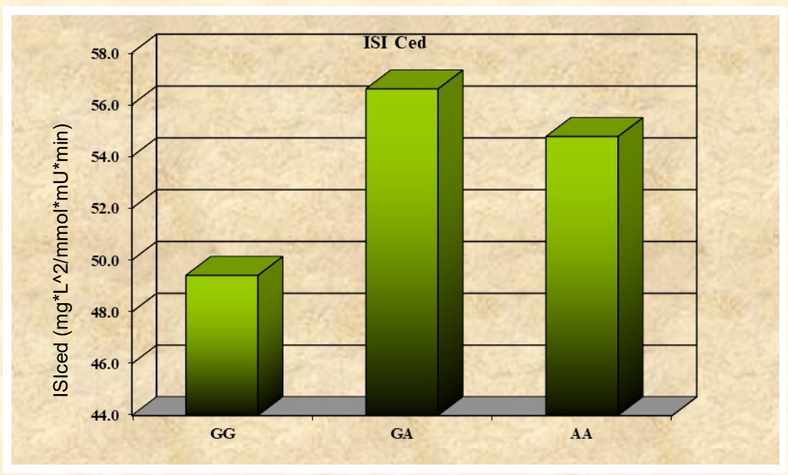
Table 1. LEP rs7799039 association with Impaired Glucose Tolerance (IGT) in RR MS patients

Genotype (n=78)	Adjusted *	
LEP, rs7799039 G/A	OR (95% CI)	p
Co-dominant genetic model	0.40 (0.17-0.92)	0.029

p* - p value adjusted for gender and other two genetic variants (LEPR rs1137101 and PGC1A rs8192678).

	RRMS patients n (%)
IGT	19 (24.36)
IR	18 (23.08)

Figure2. Association of PGC1A variant with Cederholm index



Kruskal-Wallis ANOVA, p=0.04

CONCLUSIONS

We found that genetic variants in leptin signaling pathway affect glucose tolerance and insulin sensitivity in patients with MS. As both, leptin and PGC1A have role in preventing neuronal death and reducing oxidative stress neuronal damage current results favor further investigation toward preserving cognitive status and neuroprotection in MS.

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Acknowledgment

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