Endocannabinoid system modulation in peripheral blood mononuclear cells from dimethyl fumarate-treated multiple sclerosis patients

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Background and Objectives

The **endocannabinoid system** (ECS) consists of lipid metabolites, their receptors and the enzymes implicated in their synthesis and degradation. The ECS exerts anti-inflammatory and neuroprotective properties and its modulation has the potential of being a therapeutic target in Multiple Sclerosis (MS). **Dimethyl fumarate** (DMF) is an approved drug for MS, which has immunomodulatory effects although its mechanism of action is not yet fully understood.

Objective: To test if DMF could be modulating the ECS in Peripheral Blood Mononuclear Cells (PBMCs) from MS patients.

Methods

- ✓ PBMCs from **11 Healthy Donors (HD)** and **20 MS patients** (at baseline and after 1 year of DMF treatment) were obtained by Ficoll density gradient centrifugation.
- ✓ Patients were classified into **Responder** (R) or **Non-Responder** (NR) to DMF according to No Evidence of Disease Activity (NEDA 3) at 2 years.
- ✓ The levels of the endocannabinoids **2-Arachidonoylglycerol** (2-AG), **Anandamide** (AEA), **Oleoylethanolamine** (OEA) and **Palmitoylethanolamine** (PEA) were determined by Liquid chromatography–mass spectrometry (LC-MS), and normalized to the total amount of protein.

Results

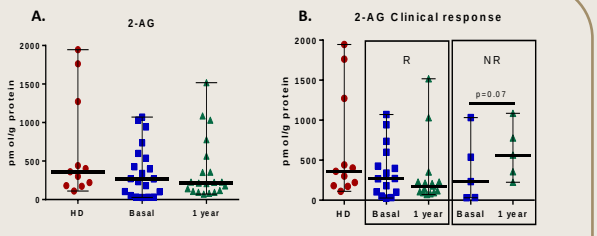

Figure 1. 2-Arachidonoylglycerol (2-AG) levels in PBMCs from Healthy Donors (HD) and MS patients. A. The median values of 2-AG were similar between HD (361.42 pmol/g protein) and patients at baseline (269.26 pmol/g protein) (p=0.23). After 1 year of treatment (218.75 pmol/g protein), no differences were found compared to baseline (p=0.70). **B.** There was a trend (p=0.07) towards an increase of 2-AG in patients that did not reach NEDA 3 on follow-up at 2 years.

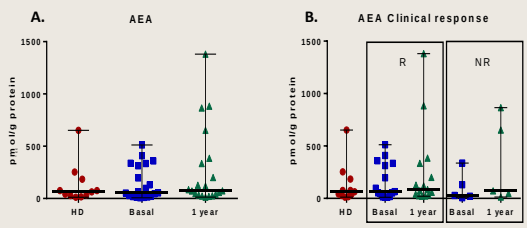

Figure 2. Anandamide (AEA) levels in PBMCs from Healthy Donors (HD) and MS patients. A. The median values of AEA were both similar between HD (63.62 pmol/ g protein) and patients at baseline (58.70 pmol/g protein). After 1 year of treatment (78.77 pmol/ g protein), no differences were found compared to baseline. B. No differences were found between the Responder and Non-responder groups.

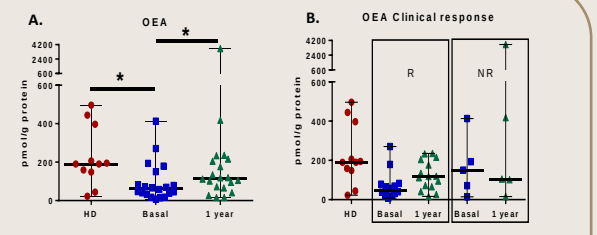

Figure 3. Oleoylethanolamine (OEA) levels in PBMCs from Healthy Donors (HD) and MS patients. A. OEA levels were lower at baseline (61.83 pmol/g protein, p=0.01) compared to HD (190.35 pmol/g protein). After 1 year, OEA levels (115.39) increased to levels similar to those of HD (p=0.04, Basal vs 1 year). **B.** No differences were found between the Responder and Non-responder groups.

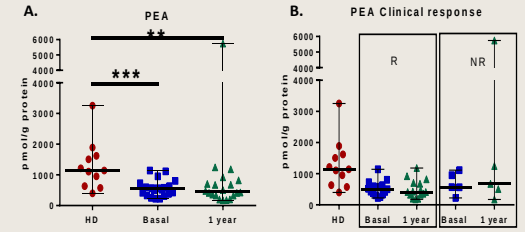

Figure 4. Palmitoylethanolamine (PEA) levels in PBMCs from Healthy Donors (HD) and MS patients.
A. PEA levels were lower at baseline (541.0 pmol/g protein) compared to HD (1140.51 pmol/g protein) (p=0.001). After 1 year, PEA levels were unchanged (449.50 pmol/g prtotein, p=0.68). **B.** No differences were found between the Responder and Non-responder groups.

Results

	MS (n= 20)	HD (n=11)
Mean Age	38.5 ± 9.7	29.09 ± 11.07
Gender (% Female)	85%	81.8%
% NEDA-3 at 2 years	75% (n= 15)	-
Disease duration (years)	6.59 ± 6.76	-
Basal EDSS	0.90 ± 0.9	-
Prior treatment & Annualized Relapse Rate (ARR)	Natalizumab: 5% (ARR: 0.53)	-
	Interferon beta: 50% (ARR: 0.35)	
	Glatiramer acetate: 5 % (ARR: 0.25)	
	Naive: 40% (ARR: 0.75)	

Table 1. Demographic characteristics od MS patients and Healthy Donors (HD)

Conclusions

- ❖ Our results show that, in our cohort, MS patients present a dysregulated ECS compared to HD.
- ❖ We have also gained insight into the mechanism of action of DMF, as it could be modulating the ECS through OEA.

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