

Poster presentation

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## Activation of soluble guanylate cyclase by nitric oxide in lymphocytes correlates with minimal hepatic encephalopathy in cirrhotic patients

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### Background

Altered modulation of cGMP levels in brain seems to be responsible for the impairment of some types of cognitive function [1]. The homeostasis of cGMP is also strongly altered in blood in patients with liver disease, who show increased plasma cGMP but reduced cGMP content in lymphocytes [2]. Activation of soluble guanylate cyclase by NO is also altered in lymphocytes of patients with liver cirrhosis [2]. This suggests that alterations in cGMP homeostasis in blood could reflect the alterations in brain and be therefore associated with the appearance of minimal hepatic encephalopathy (MHE). The aim was to assess whether there is a correlation between the alterations in different parameters involved in modulation of cGMP levels and the presence of MHE.

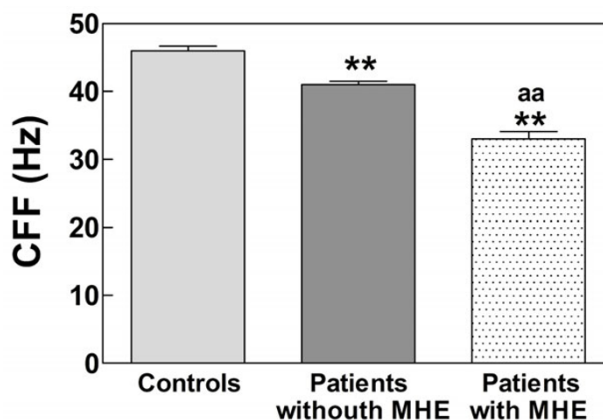
### Methods

We studied in 46 patients with liver cirrhosis and 26 controls the performance in the PHES battery of psychometric tests, critical flicker frequency (CFF), cGMP in plasma and lymphocytes, activation of guanylate cyclase by NO in lymphocytes, ammonia, nitric oxide metabolites and atrial natriuretic peptide (ANP).

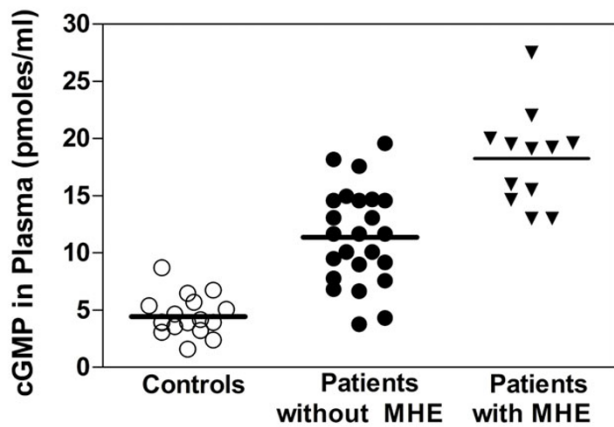
### Results

Activation of guanylate cyclase by NO in lymphocytes and cGMP in plasma were higher and CFF lower in patients

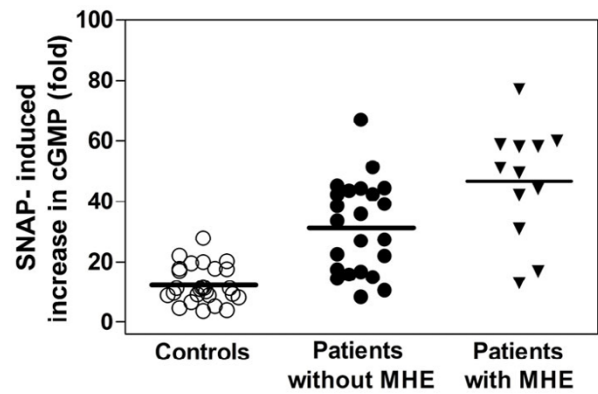
with than without MHE. Ammonia, ANP and metabolites of nitric oxide were higher in patients than in controls but were no different in patients with or without MHE (Figures 1, 2, 3, 4; Table 1).



**Figure 1**  
Critical flicker frequency.



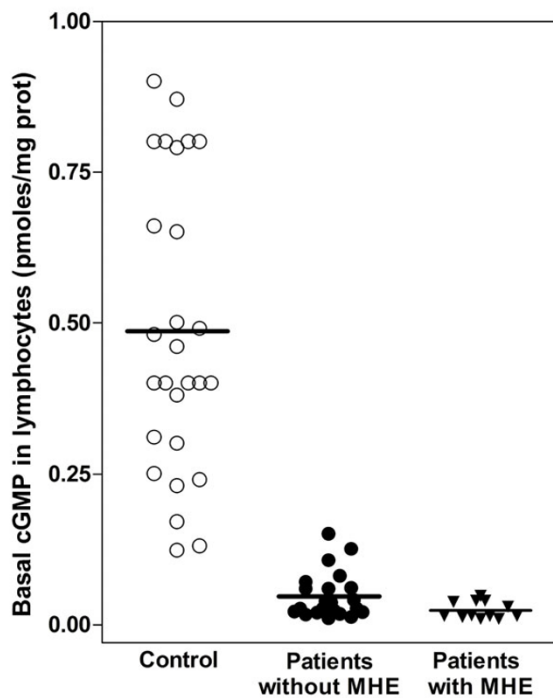
**Figure 2**  
Plasma cGMP.



**Figure 4**  
NO-induced increase in cGMP in lymphocytes.

**Conclusion**

Alteration in activation of guanylate cyclase by NO in lymphocytes correlates with PHES performance, CFF and ammonia levels (Table 2). This suggests that altered modulation of guanylate cyclase by NO in lymphocytes would reflect a parallel alteration in brain occurring in patients with MHE that would be involved in their cognitive impairment.



**Figure 3**  
Basal cGMP in lymphocytes.

**Table 1: Values of the different parameters analyzed in controls and in patients.**

PARAMETERS	CONTROLS Media ± SD (n)	PATIENTS WITHOUT MHE p vs. Control	PATIENTS WITH MHE P vs. control	PATIENTS WITH MHE p vs. without MHE
Basal cGMP in lymphocytes (pmoles/mg prot)	0.47 ± 0.15 (n = 26)	0.049 ± 0.02 (n = 22) p < 0.001 **	0.025 ± 0.015 (n = 12) p < 0.001 **	p > 0.05
SNAP-induced cGMP increase (fold)	12 ± 6 (n = 26)	31 ± 15 (n = 23) p < 0.001 **	47 ± 18 (n = 12) p < 0.001 ***	p < 0.05 *
cGMP in Plasma (µM)	4.4 ± 1.7 (n = 17)	12 ± 4 (n = 24) p < 0.001 **	18 ± 4 (n = 12) p < 0.001 ***	p < 0.001 **
Nitrates + Nitrites (µM)	22 ± 9 (n = 26)	31 ± 13 (n = 31) p < 0.05*	38 ± 14 (n = 13) p < 0.001 ***	p = 0.09 (ns)
ANP in Plasma (pg/ml)	78 ± 13 (n = 13)	119 ± 25 (n = 14) p < 0.001 **	140 ± 50 (n = 9) p < 0.001 **	p = 0.193 (ns)
Ammonia concentration (µM)	76 ± 30 (n = 23)	156 ± 86 (n = 23) p = 0.001 ***	151 ± 51 (n = 9) p < 0.001 ***	p = 0.89 (ns)
CFF (Hz)	46 ± 3 (n = 26)	41 ± 3 (n = 24) p < 0.001 ***	33 ± 4 (n = 15) p < 0.001 **	p < 0.001 **
SCORE PHES	-0.15 ± 1 (n = 26)	-0.57 ± 1 (n = 31)	-8.7 ± 2.1 (n = 15)	p < 0.001 **
Age	43 ± 12	50 ± 8	55 ± 11	p > 0.05 (ns)

**Table 2: Correlations between different parameters analysed.**

PARAMETER	CORRELATION WITH		
	PHES	CFF	AMMONIA
cGMP in plasma	NO p = 0.06, r = -0.235	YES p = 0.004, r = -0.368	YES p = 0.011, r = 0.386
cGMP in lymphocytes	NO p = 0.67, r = -0.11	YES p = 0.029, r = -0.281	NO p = 0.28, r = -0.165
Activation of sGC by NO	YES p = 0.004, r = -0.369	YES p < 0.0001, r = -0.544	YES p = 0.003, r = 0.433
Ammonia	NO p = 0.28, r = -0.156	YES p = 0.021, r = 0.333	

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