# Beta-endorphin: past, present, future

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# Beta-endorphin

It is an opioid peptide *released* by hypothalamus, pituitary gland and by lymphocytes

Its traditional *functions* are related to

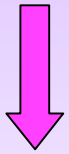
modulation of pain
mood
food assumption
endocrine secretion

*Immunomodulating functions*

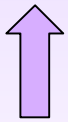
inhibition of antigen-induced-Tcell-proliferation
downregulation of proinflammatory cytokines
inhibition of IL6 and IL12 macrophage secretion

# **Beta-endorphins and** Immune system

In the immune system, endogenous opioids ( beta-endorphin) find a physiological role in the modulation of the Th1/Th2 balance.



Th1 cytokines ( IL-2, IFN-gamma)



Th2 cytokines (IL-4)

Panerai and Sacerdote, Immunology Today, 1997
Sacerdote et al. Clin Exp Immunol, 1998
Sacerdote et al. J Neuroimmunol, 1999
Sacerdote et al, Blood, 2000

# Beta-endorphins and diseases

TRENDS IN IMMUNOLOGY TODAY

Panerai and Sacerdote, 19:309,1997

**Table 1. Concentrations of BE in different situations and pathologies characterized by predominant Th1-type or Th2-type immune responses in (a) human PBMCs or (b) rodent splenocytes**

(a) Human PBMCs

| Situation/pathology | BE concentration | Th1–Th2-type response |
|---|---|---|
| HIV$^+$ | ↑ | Th2 |
| Multiple sclerosis | ↓ | Th1 |
| Rheumatoid arthritis | ↓ | Th1 |
| Crohn's disease | ↓ | Th1 |

(b) Rodent splenocytes

| Situation/pathology | BE concentration | Th1–Th2-type response |
|---|---|---|
| Stress | ↑ | Th2 |
| EAE | ↓ | Th1 |
| MLR *lpr/lpr* | ↓ | Th1 |
| Adjuvant arthritis | ↓ | Th1 |

Abbreviations: BE, β-endorphin; EAE, experimental autoimmune encephalomyelitis; HIV, human immunodeficiency virus; MLR *lpr/lpr*, autoimmune-disease-prone mice; PBMCs, peripheral blood mononuclear cells; Th, T helper.

Sacerdote et al. Clin Exp Immunol, 1998
Sacerdote et al. J Neuroimmunol, 1999
Barcellini et al, Peptides, 1993
Wiedermann et al., Clin Exp Immunol, 1992
Wiedermann et al., Brain Behav Immun ,1994

# Peripheral Blood Mononuclear Cell β-Endorphin Concentration Is Decreased in Chronic Fatigue Syndrome and Fibromyalgia but Not in Depression: Preliminary Report

*Alberto E. Panerai, M.D., ‡Jacopo Vecchiet, M.D., †Paolo Panzeri, M.D., †PierLuigi Meroni, M.D., ‖Silvio Scarone, M.D., ‡Eligio Pizzigallo, M.D., §Maria A. Giamberardino, M.D., and *Paola Sacerdote, Ph.D.

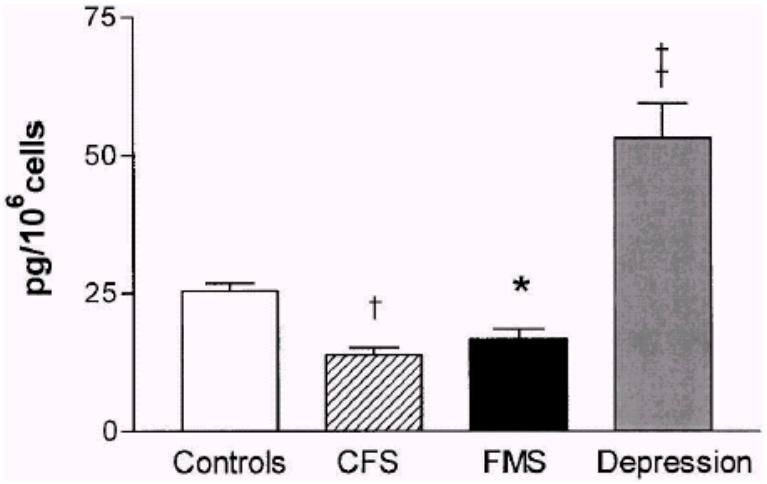
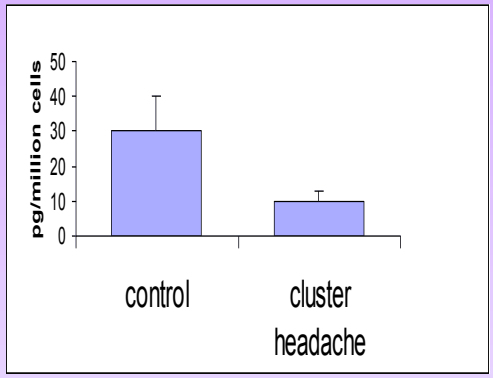
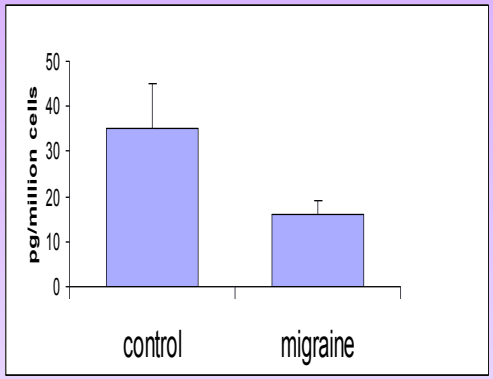


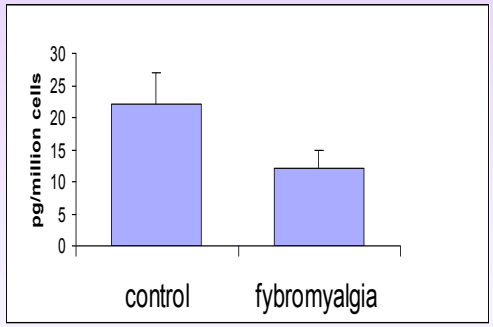

**FIG. 1.** β-Endorphin concentrations in peripheral blood mononuclear cells (PBMCs) from controls (25 ± 1.43 pg/$10^6$ cells; n = 8), patients with chronic fatigue syndrome (CFS; 13.85 ± 1.32 pg/$10^6$ cells; n = 17), fibromyalgia syndrome (FMS; 16.7 ± 1.87 pg/$10^6$ cells; n = 5), and depression (53.2 ± 6.02 pg/$10^6$ cells; n = 10). Values are mean ± SEM; *$p$ <0.01; †$p$ <0.001 for comparison with healthy controls and persons with depression; ‡$p$ <0.01 for comparison with healthy controls.

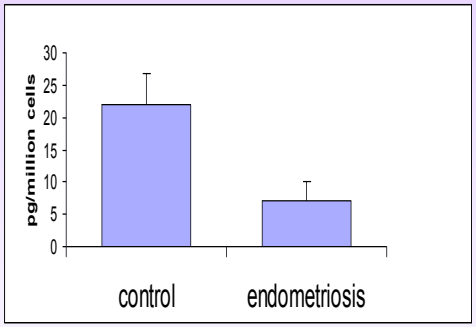
Clin J Pain, 2002

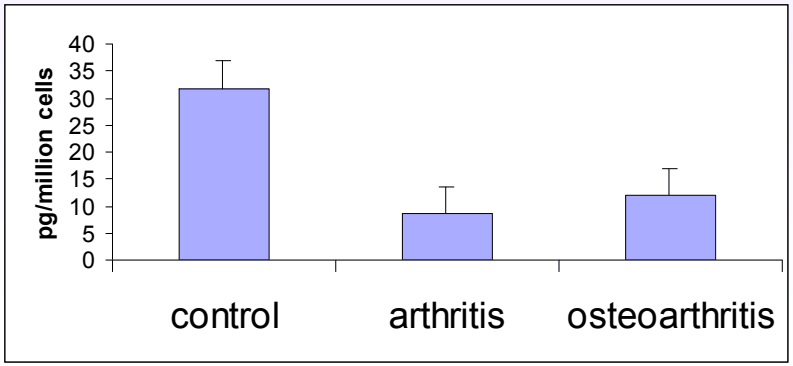
# Beta endorphin concentrations in immune cells of patients with pain




Cephalalgia,1993,1994
Clin Exp Immunol 1992
Ost.Gynecol,1993
Brain Res Bulletin,1996
Clin.J.Pain,2002

# Low BE concentrations can be permissive for development of an autoimmune disease

# **Beta-endorphins** and Multiple Sclerosis

Multiple Sclerosis is the most common immune-mediated demyelinating disease of the central nervous system

Immune system may be involved

•in the coordination of *antigen-specific attack* to myelin

or

• in a *non-specific immune activation*

Preliminary studies had documented:

Low levels of PBL Beta-endorphins in MS patients

Opioid antagonism increases EAE severity

Aim of our FIRST study was to evaluate:

endorphin level

- in stable and relapsing MS patients
- during IFNβ treatment

PATIENTS:

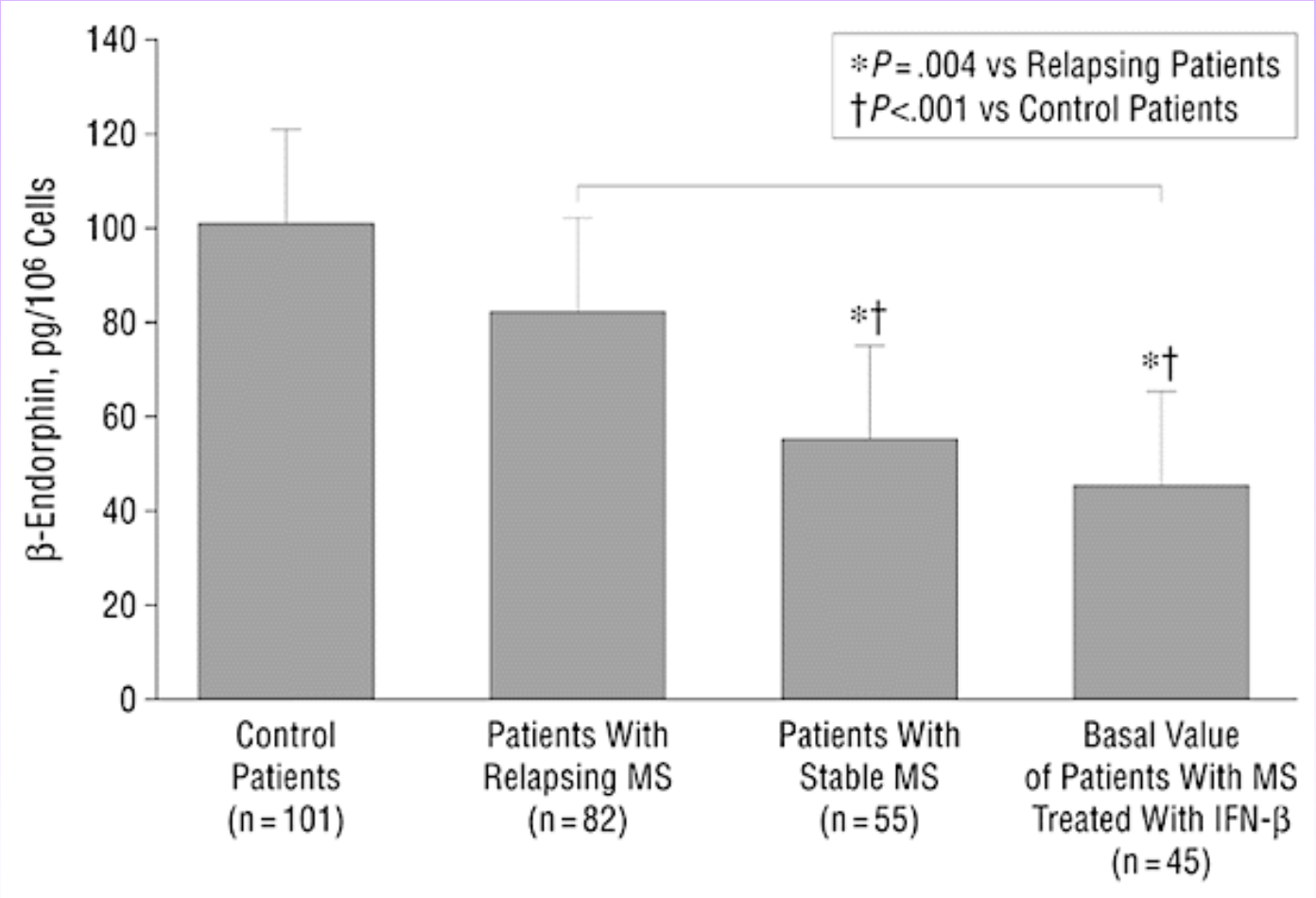
6 patients in stable phase of disease

7 patients during a clinical-relapse of disease

8 patients during IFNβ treatment

21 age and sex-matched healthy controls

## Mean {beta}-endorphin levels in peripheral blood mononuclear cells obtained from patients with multiple sclerosis (MS) and age-matched controls

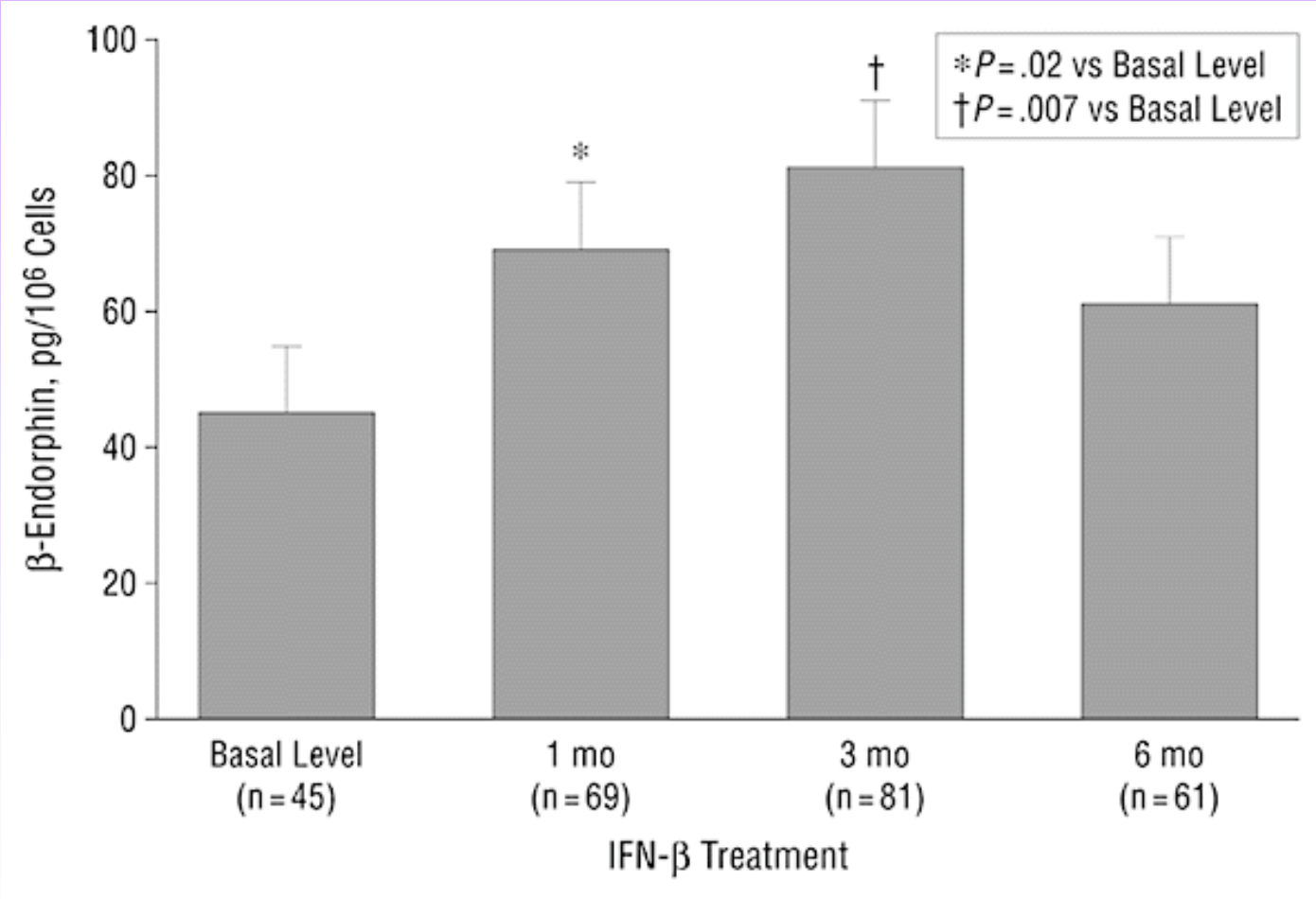



Gironi, M. et al. Arch Neurol 2000;57:1178-1181.



ARCHIVES OF NEUROLOGY

## Mean {beta}-endorphin levels in lymphocytes obtained from patients with multiple sclerosis during treatment with interferon beta (IFN-{beta})

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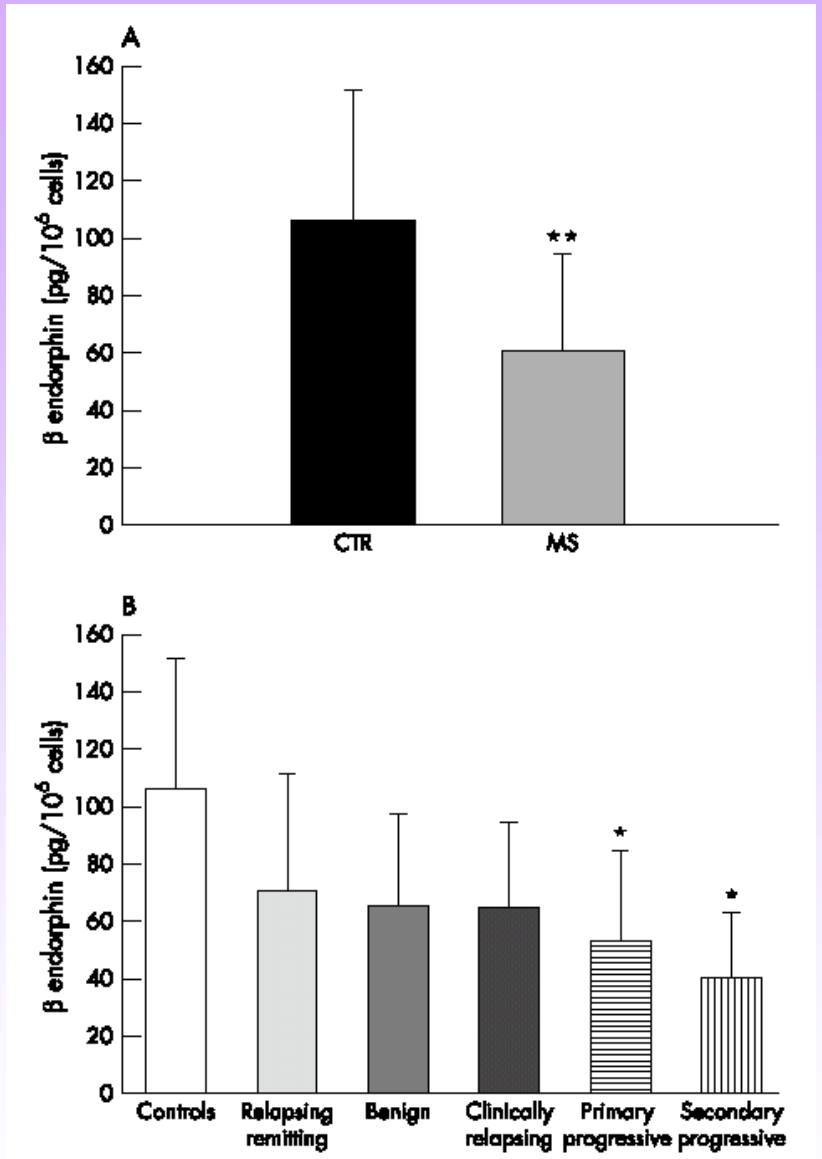


**Figure 1** (A) β Endorphin concentrations in peripheral blood mononuclear cells (PBMC) of patients with multiple sclerosis (MS) and of healthy control (CTR). (B) PBMC β endorphin concentrations in various MS clinical phenotypes. Values are mean (SD). *p<0.05; **p<0.001.

Aim of SECOND study was to investigate a role for BE in heterogeneity of MS course

Gironi et al. J Neurol Neurosurg Psychiatry 2003

## ….comments

- BE levels were lower in MS patients than in controls

- The highest BE levels were detected in relapsing group.
(a control mechanism of down-regulation?)

- The lowest BE levels were in progressive forms (PP, SP):
(absence of a protective mechanism ?)

Different mechanisms related to BE increase during IFNβ treatment
(reset of cytokine pattern:IL1, IL6)
(IFNβ-induced increase of Corticotropin-releasing hormone)

## ……and speculations

BE increase (direct or indirectly-mediated) as a natural downregulatory mechanism of inflammatory process

# Beta-endorphin and

….future

# rational of the new study

Primary Progressive MS form is

- *orphan* of effective drug
- has the highest prevalence of *fatigue,pain, spasticity*
- has the *lowest BE levels*
- a *neurodegenerative process* is supposed to be involved in pathogenesis of this form

Low Dose Naltrexone is

- documented *effective on* fatigue, pain, spasticity
- two putative mechanisms postulated for this positive effect are
  the *raise of* BE levels
  the *downregulation of the neurodegenerative process* (by inhibition of glutamate-excitotossicity)

# Aims of the study

Evaluation of:
SAFETY and TOLERABILITY of LDN

EFFICACY on spasticity, pain, fatigue

In 40 patients suffering from PP-MS

Investigate a possible correlation between BE levels and clinical evolution

# Methods

This pilot, multicentric, open-study will be divided into 3 phases:

4 weeks of prescreening
24 weeks of treatment
4 weeks of follow-up

The 40 patients enrolled will be daily *treated* with LDN at the final dose of 3.75 mg,

titration for 2 weeks:1.25 mg for 1°week; 2.5 mg for 2°week

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