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 T-cell-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. J Neuroimmunol, 1999
Sacerdote et al, Blood, 2000
Beta-endorphins and diseases

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

<table>
<thead>
<tr>
<th>Situation/pathology</th>
<th>BE concentration</th>
<th>Th1–Th2-type response</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV¹</td>
<td>↑</td>
<td>Th2</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>↓</td>
<td>Th1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>↓</td>
<td>Th1</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>↓</td>
<td>Th1</td>
</tr>
</tbody>
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<th>Situation/pathology</th>
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<tr>
<td>Stress</td>
<td>↑</td>
<td>Th2</td>
</tr>
<tr>
<td>EAE</td>
<td>↓</td>
<td>Th1</td>
</tr>
<tr>
<td>MLR lpr/lpr</td>
<td>↓</td>
<td>Th1</td>
</tr>
<tr>
<td>Adjuvant arthritis</td>
<td>↓</td>
<td>Th1</td>
</tr>
</tbody>
</table>

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. 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., ‡Pier Luigi Meroni, M.D., |Silvio Scarone, M.D., ‡Eligio Pizzigallo, M.D., §Maria A. Gamberardina, M.D., and *Paola Sacerdoti, 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.
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
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 \{\text{beta}\text{-endorphin}\} levels in peripheral blood mononuclear cells obtained from patients with multiple sclerosis (MS) and age-matched controls

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

Aim of SECOND study was to investigate a role for BE in heterogeneity of MS course.
....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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Claudio Solaro (Depart of Neurology, Genova Hospital)

And Paola Sacerdote (Depart. of Pharmacology, University of Milan)