Opioid-immune interactions in autism: 
behavioural and immunological assessment 
during a double-blind treatment with naltrexone

Renato SCIFO (a), Matteo CIONI (b), Alfredo NICOLOSI (c), Nunzio BATTICANE (b), 
Cataldo TIROLO (b), Nuccio TESTA (b), Maria C. QUATTROPANI (d), Maria C. MORALE (b) 
Francesco GALLO (e) and Bianca MARCHETTI (e)

(a) Servizio di Psichiatria; (b) Servizio di Neuropsicofarmacologia, Istituto OASI per lo Studio del 
Ritardo Mentale e l’Involuzione Cerebrale, Troina (Enna), Italy
(c) Istituto di Tecnologie Biomediche Avanzate, Epidemiologia e Informatica Medica, Consiglio 
Nazionale delle Ricerche, Milan, Italy
(d) Servizio di Neuropsicologia, Istituto di Scienze Neurologiche; (e) Istituto di Farmacologia, 
Università degli Studi, Catania, Italy

Summary. - The emerging concept of opioid peptides as a new class of chemical messengers of the neurotransmitter axis and the presence of a number of immunological abnormalities in infantile autism prompted us to correlate biological (hormonal and immunological) determinations and behavioural performances during treatment with the potent opiate antagonist naltrexone (NAL). Twelve autistic patients ranging from 7 to 15 years, diagnosed according to DSM-III-R, entered a double-blind crossover study with NAL at the doses of 0.5, 1.0 and 1.5 mg/kg every 48 hours. The behavioural evaluation was conducted using the specific BSE and CARS rating scales. NAL treatment produced a significant reduction of the autistic symptomatology in seven ("responders") out of 12 children. The behavioural improvement was accompanied by alterations in the distribution of the major lymphocyte subsets, with a significant increase of the T-helper-inducers (CD4+CD8+) and a significant reduction of the T-cytotoxic-suppressor (CD4+CD8-), resulting in a normalization of the CD4/CD8 ratio. Changes in natural killer cells and activity were inversely related to plasma β-endorphin levels. It is suggested that the mechanisms underlying opioid-immune interactions are altered in this population of autistic children and that an immunological screening may have prognostic value for the pharmacological therapy with opiate antagonists.

Key words: autism, opioid peptides, naltrexone, immune function.

Riassunto (Intervento tra peptidi oppiacei e sistema immunitario nell'autismo: determinazioni comportamentali ed immunitarie durante un trattamento doppio cieco con naltrexone). - Il ruolo emergente giocato dai peptidi oppiacei endogeni quali messaggeri chimici nel controllo dell'asse neuro-endocrino-immunitario, ed il loro coinvolgimento in diverse patologie psichiatriche, ci hanno indotto a studiare l'effetto di un trattamento cronico con il potente antagonista recettoriale, naltrexone (NAL) nell'autismo infantile, correlando dati comportamentali ed effetti a carico del sistema immunitario. Il tomo oppiaceo endogeno veniva monitorato mediante il dosaggio della β-endorfina plasmatica. Dodici pazienti autistici (DSM-III-R) di età compresa tra i 7 e 15 anni venivano trattati, in doppio-cieco e crossover, con NAL alle dosi di 0.5, 1.0, e 1.5 mg/kg ogni 48 ore, e seguiti sul profilo comportamentale usando specifici rating scales (BSE e CARS). Il trattamento con NAL produceva una riduzione significativa della sintomatologia autistica in 7 pazienti identificati come "rispondenti". Sul versante immunitario, il blocco cronico dei recettori oppiacei determinava un aumento significativo delle sottopopolazioni T-helper-inducers (CD4+CD8+) ed una concomitante diminuzione dei T-citotossici-suppressori (CD4+CD8-), riportando così alla norma il rapporto CD4/CD8. Le alterazioni nella popolazione di natural killer (NK) erano accompagnate da modificazioni dei livelli di β-endorfina plasmatica. Gli effetti comportamentali ed immuniossuviati durante il trattamento con NAL in questi pazienti suggeriscono quindi l'ipotesi di una disfunzione del tomo oppiaceo nell'autismo e suggiscono uno screening immunitario quale fattore prognostico per la farmacoterapia con antagonisti recettoriali degli oppiacei.

Parole chiave: autismo, peptidi oppiacei, naltrexone, sistema immune.

Introduction

There is a growing body of evidence that the immune and the central nervous systems interact, and reciprocally influence each other [1-5]. Among the neuropeptides considered to be involved in the bidirectional regulation of the neuroimmune functions, the endogenous opioids, and in particular β-endorphin (BEP), have received more attention [6-9]. The potential immunomodulatory role of endogenous opioids has emerged in the light of in vitro and in vivo findings showing: a) the presence of specific opioid receptors in cells of the immune system [6, 8-10]; b) the production of opioid peptides by cells of the immune system [11, 12]; and c) the direct interaction of
opioid peptides with cells of the immune system, resulting in a modulation of the immunological activity [9, 12, 13, 5]. Opioid peptide modulation of immune cells include effects on T-lymphocytes, B-lymphocytes, natural killer (NK) cells, granulocytes and monocytes [8, 9, 14-16]. Accordingly, a number of immunological functions, including chemotaxis, phagocytosis, mitogen-induced proliferation, active T-cell rosette formation, T-cell suppressor activity, natural cytotoxicity, and antigen-induced antibody response are directly influenced by opioid peptides. The possible role of an abnormal brain opioid activity in the genesis of autistic symptoms has previously been suggested and this subject has been reviewed by different investigators [17-25]. On the other hand, an immunological basis for the etiologic causes of autism has also been proposed [7, 8, 26-37]. Taken together the assumptions that: a) the opioid system plays a crucial role in cognitive and immunological functions [6-9]; and b) the endogenous opioid peptides are present in excess in autism [17-25]; then pharmacological reduction of the opioid tonic by treatment with an opiate antagonist [23-25, 38-40] might counteract some of the behavioral and immunological disturbances observed in autistic individuals. In our previous study [8] we have found a correlation between the plasma levels of the opioid peptide, BEP, and the NK cells in infantile autism and suggested the possibility to improve the pharmacologic therapy with opiate antagonists by an immune screening of the autistic patients. Since, to our knowledge, alterations of plasma β-endorphin levels have never been correlated with immunological parameters under naltraxone (NAL) therapy in autism, in the present work we, then, sought to evaluate both behavioral and biochemical determinations, at different time intervals during a long-term blockade of opiate receptors in a double-blind crossover study with the opiate antagonist, NAL.

Methods

Subjects

Twelve children (10 males and 2 females; range of age 7-15 years) with autism were included in this study. Four of them were home reared whereas the other eight individuals were institutionalized for a short period at the OASI Institute, Troina (Enna), Italy. Diagnosis was established according to the DSM-III-R, using the specific rating scales CARS (childhood autistic rating scale) [41] and BSE (behavioural summarized evaluation) [42], by an evaluation performed independently by a child psychiatrist and a psychologist. A complete agreement between the psychiatrist and the psychologist was required for diagnosis. Only three children could make use of verbal language (two of them only echolalic), only one showed a good cognitive level (IQ > 50) while the others presented severe (IQ < 34) or very severe (IQ < 20) mental retardation, in three case. Two subjects, a boy and a girl, presented also dramatic self injurious behaviour (SIB). Only autistic individuals participated to the study. Therefore, in order to exclude associated specific neurological syndromes (dissmetabolic and/or genetic), after the neuropsychiatric assessment, the individuals with autism were further examined by a chromosomal analysis in a folic-acid depleted medium, a complete metabolic screen, CAT scan and electrophysiological examinations (EEG and auditory brain stem evoked potentials). Patients were drug free for 6 weeks. Twelve individuals with mental retardation of unknown etiology, age and sex matched (10 males and 2 females, range of age 7-15 years), were studied as a control group for the baseline period of the study. None of them was on any drug treatment. Written consent was obtained by the parents of all subjects participating to this study.

Protocol of treatment

The individuals with autism were treated in a double-blind placebo crossover design with NAL (antaxone, administered in capsules once every 48 hours in single evening doses; placebo administered in the same capsules containing lactose and magnesium stearate). They were randomly divided in group A and B. For both groups the experimental protocol started with a baseline period of one week. Then, the group A received NAL at different doses (0.5 - 1.0 - 1.5 mg/kg) for 15 weeks and successively the placebo for other 15 weeks. On the other hand, the group B received firstly the placebo and then the NAL medication. Each dose of NAL was given for 5 weeks with this sequence: I (0.5 mg/kg), II (1.0 mg/kg), III (1.5 mg/kg). In order to determine BEP plasma levels, immunological parameters, SGOT-SGPT, γ-GT and creatinine levels, venous blood samples were collected at 9:00 p.m., for the whole experimental protocol (2 samples for the baseline period, 2 for the placebo treatment and 2 for each of the NAL doses). The behavioural assessment was carried out by video-taping the children in a semi-structured playroom, in the presence of the mother when individuals were outpatients, or in presence of one educator or of the child psychiatrist (R.S.) when they were inpatients. At first, the spontaneous activity was examined and then the adult encouraged the child to make contact, to explore and play with toys. By observations of video-tapes, a “blind psychologist” assessed the behaviour of children by means of CARS [41] and of BSE [42]. The behavioural assessment was repeated every 5 weeks, at the end of each treatment cycle, and concomitantly venous blood samples were collected (12 hours after the evening administration of NAL or placebo).
Lymphocyte subset phenotyping

The distribution of lymphocyte subsets in autistic patients was monitored at different time intervals before (baseline) and during the placebo and NAL therapy, with two blood samples/patient for each (basal, placebo and NAL 0.5, 0.1, 1.5 mg/kg) condition. Cells labeled with monoclonal antibodies (MoAbs) (Table 1) for cytofluorimetric analysis were prepared from whole blood following standard methods and as previously described in full details [43]. Briefly, peripheral blood lymphocytes (PBL) were harvested and washed by centrifugation at 200 x g in physiologic-buffered saline (PBS) 0.1% bovine serum albumine (BSA). Pellets were resuspended with 50 ml of one of the solutions containing the appropriate dilutions of MoAbs. Antibodies were titrated to optimal concentrations at which no cellular aggregate was detected.

Flow cytometry

Cells were incubated with antibodies on ice for 45 min, washed twice, and fixed by incubating for 15 min in 1 ml 0.5% paraformaldehyde [43, 44]. The cells were quantitated for green fluorescence distribution at the rate of 100 cells/s. For each fluorescent distribution, a clear region between the positively and negatively stained cells was established. The data are expressed as percentages (%) of peripheral blood monocytes positive to the used MoAbs.

Plasma BEP levels

Plasma levels of BEP were measured using an immunoassay system for the direct measurement of human BEP, with a solid phase, two sites immuno-radiometric assay (IRMA, Nichols Institute Diagnostic, San Juan Capistrano, CA 92675) [8] with a sensitivity of 10 pg/ml. Blood samples were collected between 9:00 and 10:00 a.m. at two time intervals during baseline, placebo, and NAL therapy periods. All samples of each subject (8-10 samples) were assayed in duplicate, and at the same time. The intra- and inter-assay mean variability never exceeded the 2.5%.

Data analysis

The statistical analysis of the biological determinations has been performed both for each subject and as a mean ± SD of values for the groups A and B or for the groups of subjects “responders” or “not responders” to the therapy. Furthermore, the multiple range test of Duncan-Kramer, the analysis of variance (ANOVA), the Newman-Keuls post-hoc test were used. The ratings of CARS [41] and BSE [42] were analyzed by an analysis of variance and paired t-test for the three levels of NAL (0.5, 1.0, 1.5 mg/kg once every 2 days), placebo and baseline ratings.

Results

Behavioural performances in autism under NAL therapy

Fig. 1 (left panel) shows that, when symptomatology was evaluated by the BSE, NAL ratings were significantly lower (0.5 mg/kg, F 16.82 = p < 0.005; 1.0 mg/kg, F 14.56 = p < 0.005; 1.5 mg/kg, F 15.02 = p < 0.005) than those recorded during the baseline period. Moreover, NAL significantly reduced the symptomatology in comparison with placebo ratings (F 8.99, p = 0.005), while the difference between placebo and baseline ratings is not significant (F 0.85, p = 0.4). On the other hand, Fig. 1 (right panel) shows that CARS is a less sensible tool for the evaluation of changes induced by the experimental protocol. In fact, NAL therapy induced an overall reduction of ratings, but the only significant changes were observed at the dose of 1.0 mg/kg (F 6.64, p < 0.05) in comparison to the baseline period. No significant differences have been observed between NAL and placebo or between placebo and baseline ratings.

---

Table 1. - Monoclonal antibodies employed in the study

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cluster of differentiation</th>
<th>Predominant reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu 4</td>
<td>CD3</td>
<td>T cell antigen receptor complex</td>
</tr>
<tr>
<td>Leu 3</td>
<td>CD4</td>
<td>T helper/inducer cells</td>
</tr>
<tr>
<td>Leu 2</td>
<td>CD8</td>
<td>T cytotoxic/suppressor cells</td>
</tr>
<tr>
<td>HLA-DR</td>
<td></td>
<td>B cells, monocytes, activated T cells</td>
</tr>
<tr>
<td>Leu 8</td>
<td>CD28</td>
<td>T cells, B cells, monocytes</td>
</tr>
<tr>
<td>Leu 7</td>
<td>CD57</td>
<td>T cell and NK subsets</td>
</tr>
<tr>
<td>Leu 11</td>
<td>CD16</td>
<td>IgG Fc receptor III on NK cells and neutrophils</td>
</tr>
<tr>
<td>Leu 19</td>
<td>CD56</td>
<td>NK cells, cytotoxic T cells subsets</td>
</tr>
<tr>
<td>Leu 5b</td>
<td>CD2</td>
<td>E rosette receptor associated</td>
</tr>
<tr>
<td>Leu 17</td>
<td>CD38</td>
<td>NK cells, activated T cells, B cell subset</td>
</tr>
<tr>
<td>Leu 12</td>
<td>CD19</td>
<td>B cell</td>
</tr>
</tbody>
</table>

Monoclonal antibodies (MoAbs) were purchased from Becton Dickinson (Mountain View, CA).
Fig. 1. - Behavioural evaluation under placebo and naltrexone therapy in autism. Total scores (index of autistic behaviour) at BSE and CARS after base line are illustrated. Results represent the mean ± SEM.

Fig. 2. - Individual responses in total scores at BSE. The figure illustrates the difference between the total score at the BSE in basal conditions (0) and the mean response (0.5; 1.0 and 1.5 mg/kg) under naltrexone and placebo for each subject for patients randomly assigned to group A (basal-naltrexone-placebo) and B (basal-placebo-naltrexone).

Seven children were identified as “responders” by analyzing the responses to NAL therapy for each subject (Fig. 2). Then, a subject was considered as “responder” when the difference of ratings between NAL and placebo was equal or superior to 5 scores at both CARS and BSE scales for all 3 doses of NAL. The score difference of five has been arbitrarily identified in order to exclude differences of improvement between NAL and placebo, that were not clear-cut enough. Four of the “responders” were of group A (NAL-placebo) and three of group B (placebo-NAL). Interestingly, three of them (group A) showed a marked reduction of both CARS and BSE ratings at the doses of 0.5 mg/kg (2 subjects) and 1.0 mg/kg (1 subject). The other four subjects “responders” showed a rating reduction only at the BSE. Interestingly, in all the responders the score reduction of BSE ratings
was for the items 1-2-3-4-19-20, which according to the reliability study of Barthelemy [42] are the more specific items for autistic symptomatology of this scale. In this subgroup, the best behavioural improvement was observed in one girl, at the three doses, and in the other three children at the dose of 1.5 mg/kg. It seems important to mention that in the “responders” of group A a positive clinical reaction to the placebo was observed in two patients. Such effect might be due to the known [8, 45] long lasting effects of NAL, and since no wash out period preceded the placebo cycle, a possible residual effect of the drug is hypothesized.

Lymphocyte subset distribution during NAL therapy

The analysis of lymphocyte subsets during NAL therapy revealed a high variability between individuals with autism. The immunological profile was consistently modified under NAL therapy, with some differences according to the schedule (groups A or B) and the doses of NAL. A previous study of the immunological profile of these autistic children in basal conditions [8] revealed significant alterations in the T-helper (CD4^+CD8^-) and T-suppressor (CD4^+CD8^+), with a consequent inversion of the CD4/CD8 ratio, an increase in the immature double positive T cells (CD4^+CD8^-) and marked changes in the natural killer (NK) cell population, when values were compared to measures obtained in a population of age- and sex-matched mentally retarded children.

When each patient was analyzed according to both biological measurements and clinical improvement, the group of “responders” showed some peculiar immunological characteristics (Fig. 3). Irrespective of the schedule (group A or B) of treatment, patients with different degrees of improvement of their autistic behaviour showed a significant (p < 0.01) increase in the
T-helpers (Fig. 3, panel 1), a significant (p < 0.01) decrease in T-suppressor subsets (Fig. 3, panel 2), with a consequent normalization of the CD4/CD8 ratio (Fig. 3, panel 4). More specifically, an overall increase in the T helper-inducer subset and a decrease in T cytotoxic subpopulations accompanied the positive effect of NAL. Such effects were significant especially at the doses of 0.5 mg/kg and/or 1.0 mg/kg (Fig. 3, panels 1 and 2). Interestingly enough, NAL treatment, irrespective of the doses used, sharply reduced the high percent of immature T cells and the double positive CD4*CD8* (Fig. 3, panel 3), which represent immature thymocytes that naturally undergo negative selection and are almost absent in the PBMC of normal individuals. It was, however, possible to observe that in the “responders” of group A the differences between NAL and placebo were not always statistically significant, compared to the differences measured in group B, where the effect of NAL vs placebo was highly significant (p < 0.05; p < 0.01) at each dose studied. In analogy to what suggested for the behavioural aspect, such differential effect of NAL might pertain to the residual effect of the drug in group A, masking the real immunological condition under the placebo cycle.

**Plasma BEP in autistic children during NAL therapy**

As already outlined in the study in basal conditions [8], circulating BEP levels were extremely heterogeneous at the start of the study, with very low or high plasma concentrations of the opioid peptide, suggesting different degrees of opioid system dysfunction. The placebo treatment, when administrated just after the baseline, produced in a number of patients a reduction of plasma BEP concentrations, or no significant effects. NAL therapy produced different effects according to the BEP basal levels. In Fig. 4, the “responders” individuals have been arbitrarily divided according to low or high levels of NK cell population and BEP levels during the baseline period. Patients with very low NK percentages (3 patients in group A and 2 patients in group B, Fig. 4 top panels 1-2) showed a response to NAL characterized by an increase in NK cells, with a maximal effect with doses of 0.5 and 1.0 mg/kg. Patients with very high NK and with parallel changes in their CD3/CD8* (representing cells with high NK activity, (1 patient in group A and 1 patient in group B, Fig. 4 bottom panel, 3-4), showed a marked decrease during NAL, while the opposite was determined for patients with very low NK percentages which showed a sharp decrease in both NK and CD3/CD8* activities. Responders (within groups A and B) were characterized by an inverse reciprocal correlation between BEP levels and NK activity. The number of patients, however, does not permit to statistically analyze the data, nor to draw a conclusion, but to observe that levels of BEP were inversely related to the distribution of the NK cell population during NAL treatment.

**Behavioural and biochemical determinations under NAL therapy in non-responders**

Generally, NAL therapy produced effects on both the biological and behavioural aspects of the autistic symptomatology of this cohort of children, however, not all the effects were statistically significant, other were very low, and were not considered as positive. Then, this group of patients with a low or absence of response was considered as “non-responders”. Some typical features characterized the non-responding group. From an immunological point of view, the non-responders started with very low CD4* percentages and higher CD8* subset, the double positive CD4* CD8* were also very high. Plasma BEP was mostly on the low range, but also patients with high BEP were observed. NAL therapy did produce an improvement of that picture, but the measured effects in the distribution of the different T lymphocyte subclasses, did not reach a statistical significance, and the CD4*/CD8* ratio still remained very low. The NK population was not significantly modified in this subgroup of patients.

**Discussion**

This study shows that it is possible to influence some behavioural and immunological alterations present in a subpopulation of autistic children by chronic blockade of opioid receptors with a potent opioid antagonist, supporting the concept of an opioid-immune link in autism [8, 9].

The efficacy of pharmacological reduction of opioid tone with NAL in autism, has been firstly explored in a double-blind trial by Herman [37] with evidence of a decrease of total SIB frequency. Successive, both double blind [23] and open trials [25, 39] showed tranquilizing effects, reduction of stereotypies, increased verbal production, improvement of social behaviours. In these studies, no major side effects were reported at doses ranging from 0.5 mg/kg to 2 mg/kg, administrated either daily or every two/three days. There is only one report by Lensing [45], on a long term (one year) trial, with NAL, but the experimental design was not controlled, nor double blind and with placebo. To assess critically the short-term efficacy and safety of NAL in autistic children, and its effects on discrimination learning, Campbell *et al.* [39] recently conducted a trial and observed a significant reduction of hyperactivity, with no serious untoward effects, together with a suggestion of a beneficial effect on decreasing self-injurious behaviour. In our study, NAL therapy induced clinical changes that BSE showed with a greater precision than CARS, the latter giving a more general picture of the autistic condition. The clinical improvement appears evident in the reduction of social withdrawal and stereotypies, improvement of eye contact
and attention, while it is not as strong as the effect of haloperidol on aggressiveness and hyperactivity. In the individuals “responders” the clinical improvement was dramatic with a marked increase of attention and of “proximity seeking behaviour”, and affective lability was also reduced. None of children showed any evidence of sedation. At the dose of 1.5 mg/kg we recorded a worsening of behavioural ratings, in comparison with the other doses, in 6 over 12 children, both responders and non-responders. It seems interesting to notice that two different patterns of response to NAL appeared to correlate to either the BEP or NK responses. In patients showing major increase in SIB (specifically described by some items of CARS and BSE) and with extremely high BEP levels and mental retardation, the clinical evidence of a decreased self-aggressive behaviour appeared to accompany the lowering of BEP profile. On the other hand, in patients with lower self-agressivity and low BEP, inhibition of autistic-like behaviour seemed to parallel the NK response. In these patients it was also possible to observe that the 1.0 mg/kg dose was the most effective, while at 1.5 mg/kg, an inversion of the positive behavioural response was observed. Such reversal was accompanied by a similar reversal in the NK response and with constantly high BEP plasma levels.

Some immunological abnormalities observed in autism have been described in autoimmune diseases including systemic lupus erythematosus (SLE) [46] multiple sclerosis [47-49] and in genetic mental retardation (Trisomy 21) [43]. Furthermore, antibodies reactive to myelin basic protein have recently been detected in the sera of autistic children [34]. Therefore, the immunological abnormalities as well as the abnormal levels of BEP observed in the present study might represent epiphenomena not specifically related to autism. However, the positive behavioural response to NAL in more than one half of the population studied with a concomitant positive modulation in the same patients of the abnormal immune parameters, suggest a possible correlation between the blockade of opioid receptors, the behavioural performance and the immune homeostasis in autistic children. Then, in view of these results, it seems tempting to suggest that the analysis of immune markers might serve as a window on the opioid system and that an immune screening might optimize the pharmacologic therapy with opiate antagonists, in the autistic patients. In fact, although the limited number of patients do not permit a definitive conclusion, a suggestive immune phenotype may be detected in clinically “responders” and “non responders” individuals. The relevance of helper/Suppressor disturbances in autism is presently unknown, but might be associated with the development of cell-mediated and humoral immune responses against various elements of the nervous system, allowing the activation of self-reactive T cells and B clones. The observation of differential effects of NAL on the NK cell population, which is either positively or negatively regulated by opioids [8, 9, 14-16, 50] seems intriguing. Natural killer cells comprise a subpopulation of lymphocytes functionally defined by their ability to specifically lyse select tumor and virally infected cells, and NK cell lytic function is sensitive to cytokines and neuroendocrine mediators [14-16]. A variety of stressors produce prolonged opioid release and a simultaneous suppression of NK activity, and this has lead to the suggestion of the development of tolerance to the acute effects of opioid on NK cell activity [16]. This is of interest also in the light of a behaviourally conditioned modulation of NK cell activity [51]. The opposite pattern of NK and opioid levels in autistic children might, then,
indicate different degrees of tolerance to chronic exposure to the opioid peptides due to receptor down- or up-regulation. The present study suggests that there are critical doses at which NAL results significantly effective in modifying both behavioural and biochemical parameters. Some evidences of decreasing effects at the higher doses might indicate a dose-dependent action with major selectivity for opioids receptors at low doses, according to the hypothesis of Zagon and McLaughlin [52-53] who suggest a similar inhibitory or stimulatory effect on opiate receptors. On the other hand, the schedule of administration of the opioid antagonist with regard to the placebo cycle seems also to interfere with the measured (behavioural and immunological) effects of the drug. Changes in receptor sensitivity to the endogenous opioid peptides after chronic blockade of opioid receptors have already been described [8], and may form part of the mechanisms responsible for the residual behavioural and immunological effects measured in patients of group A.

In summary, some behavioural and immune alterations present in a subpopulation of autistic children may be positively influenced by treatment with the opiate antagonist, NAL, and a specific "immune phenotype" in clinically responder patients is suggested. These data support an opioid mechanism for some of the cognitive and immunological dysfunctions present in a subgroup of autistic individuals that may have a prognostic value during a long-term pharmacotherapy with NAL. A better understanding of opiate-mediated immunomodulation which integrates both autocrine and neuroendocrine aspects may provide the rationale for patient selection for treatment with opiate antagonists.

Received on 25 October 1995. Accepted on 20 March 1996.

REFERENCES


