The EAE-associated behavioral syndrome: II. Modulation by anti-inflammatory treatments

Y. Pollak, H. Ovadia, E. Orion, R. Yirmiya

*Department of Psychology, The Hebrew University of Jerusalem, Mount Scopus, Jerusalem 91905, Israel
bDepartment of Neurology, The Agnes Ginges Center for Human Neurogenetics, Hadassah University Hospital, Jerusalem, Israel

Received 27 June 2002; received in revised form 30 December 2002; accepted 10 February 2003

Abstract

EAE is associated with sickness behavior symptoms that are temporally correlated with inflammatory processes. To further elucidate the role of inflammatory mediators in the behavioral syndrome, EAE mice were injected daily with anti-inflammatory drugs, beginning at disease onset. Dexamethasone or interleukin-1 (IL-1) receptor antagonist or the prostaglandins synthesis inhibitor indomethacin attenuated the behavioral symptoms. Administration of the tumor necrosis-factor \( \alpha \) (TNF-\( \alpha \)) synthesis inhibitor pentoxifylline or targeted deletion of the type I TNF receptor had no behavioral effects whereas administration of pentoxifylline in IL-1ra-treated mice further reversed the behavioral depression. These findings demonstrate the critical involvement of pro-inflammatory cytokines and prostaglandins in the EAE-associated behavioral syndrome, and may have implications for understanding and treating the neuropsychiatric disturbances in multiple sclerosis (MS) patients.

Keywords: EAE; Sickness behavior; Pro-inflammatory cytokines; Prostaglandins; Anti-inflammatory drugs; Multiple sclerosis

1. Introduction

EAE is an autoimmune disease of the central nervous system (CNS), in which CD4 Th1 cells are activated against self-myelin proteins and insult the myelin sheaths within the brain and spinal cord. This insult results in ascending motor and sensory deficits. The clinical episodes of EAE are associated with a behavioral syndrome consisting of anorexia and loss of body weight, reduced consumption of a sweet solution and decreased social investigation (Pollak et al., 2000). These behavioral alterations were termed EAE-associated behavioral syndrome or EBS (Pollak et al., 2002). Previous research revealed a correlation in time between phases of the EBS and the expression of the pro-inflammatory cytokines interleukin-1\( \beta \) (IL-1\( \beta \)) and tumor necrosis-factor \( \alpha \) (TNF-\( \alpha \)). Other EAE-related phenomena corresponded only partially to the behavioral phases, e.g., motor impairment began 1–2 days after the initiation of the behavioral alterations and sustained for several days after the behavioral recovery; onset of infiltration into the brain and of the increase in prostaglandin \( \mathrm{E}_2 \) (PGE\(_2\)) production within several brain areas coincided with the onset of the behavioral syndrome, but both continued following behavioral recovery (Pollak et al., in this issue).

Sickness behavior is a common phenomenon accompanying infectious and inflammatory diseases, as demonstrated in animals and in humans by administration of lipopolysaccharide (LPS), Mycoplasma fermentans, HIV-gp120, influenza virus, as well as many other pathogens and toxins (Kozak et al., 1997; Szechtman et al., 1997; Swiergieł et al., 1997; Connor and Leonard, 1998; Maier and Watkins, 1998; Yirmiya et al., 1999a,b; Dantzer, 2001; Barak et al., 2002). Pro-inflammatory mediators in general, and IL-1, TNF-\( \alpha \) and PGE\(_2\) in particular, were implicated as mechanisms mediating sickness behavior in several models (Connor and Leonard, 1998; Maier and Watkins, 1998; Yirmiya et al., 1999b, 2000; Dantzer, 2001; Larson and Dunn, 2001). The aim of the present study was to further establish the role for these inflammatory mediators in the behavioral alterations associated with EAE. To this aim, we examined the EBS in mice that were treated with the steroid anti-inflammatory drug...
dexamethasone, which attenuates cytokine production (Barnes and Adcock, 1993), as well as more specific inhibitors of IL-1, TNF-α and PGE₂, including IL-1 receptor antagonist (IL-1ra) which blocks the effects of IL-1 (Dinarello, 2000), pentoxifylline, which blocks the synthesis of TNF-α (Windmeier and Gressner, 1997), and indomethacin, which blocks the synthesis of prostaglandins from arachidonic acid by inhibiting cyclooxygenase (COX) (Lupulescu, 1996).

The most popular model of sickness behavior is the one induced by administration of LPS, the active component of gram-negative bacteria cell wall. Using this model, a role for pro-inflammatory cytokines and prostaglandins in mediating sickness behavior was established (Connor and Leonard, 1998; Maier and Watkins, 1998; Yirmiya et al., 1999b; Dantzer, 2001; Larson and Dunn, 2001; Reichenberg et al., 2001). To enable a comparison between different models of sickness behavior, the protocols used to manipulate cytokine actions in EBS were subsequently examined in LPS-treated mice.

2. Methods

2.1. Subjects

Subjects were female SJL/J or C57Bl/6 mice (Harlan–Sprague–Dawley, USA) or C57Bl/6 mice with targeted deletion of the p55 TNF receptor gene (TNFR1−/−) (Jackson Laboratories). Mice (7–12/group) were 8–12 weeks in age. Animals were housed individually in constant room temperature (23 ± 1 °C), and were provided with food, water and 2% sucrose solution ad libitum. Treatments and measurements were conducted during the dark phase of a reversed 12 h light–dark cycle (lights off at 8:30 AM).

2.2. Active induction and clinical evaluation of EAE

In most of the experiments, EAE was induced in SJL/J mice by s.c. inoculation with 150 μg mouse proteolipid protein, PLP 139-151, emulsified in complete Freund’s adjuvant (CFA) (1:1). In addition, 300 ng Bordetella pertussis toxin was injected i.p. on the day of immunization. Because this protocol does not produce EAE in C57Bl/6 mice, in experiments with this strain, mice were inoculated s.c. on days 0 and 7 with 300 μg mouse myelin oligodendrocyte glycoprotein, MOG35-55, emulsified in CFA (1:1). In addition, 500 ng of B. pertussis toxin was injected i.p. on days 0 and 3.

The severity of the disease was scored on a scale of 0 to 6 as follows: 0 = no neurological signs; 1 = tail weakness; 2 = tail paralysis, 3 = loss of righting reflex (the mice had difficulty to turn over after being laid down on the back, but no observed locomotive difficulties); 4 = hind limb paresis/paralysis (hind limbs are dragged); 5 = quadriplegia (immobility) and 6 = death of the animal. Behavioral data of either resistant mice (which did not develop EAE) or mice that could not move (i.e., clinical score>4) were not analyzed.

2.3. Injections

Dexamethasone (Sigma, Israel, 3 mg/kg i.p.) was used as a potent anti-inflammatory treatment. To specifically inhibit TNF-α synthesis, 10 or 100 mg/kg pentoxifylline (Sigma), dissolved in saline, were administered. To specifically inhibit the effect of IL-1, mice were injected with IL-1 receptor antagonist (IL-1ra, Amgen, USA) dissolved in saline at doses of 10 or 100 mg/kg. Indomethacin was used as an inhibitor of COX. Indomethacin (10 mg/kg), suspended in 10 ml/kg saline was injected s.c. To rule out direct psychopharmacological effects of the injections, the same materials and doses that were used in the following experiments were examined in naive healthy mice. None of these compounds had any significant effect on any of the behavioral variables (data not shown).

In a separate series of experiments, 50 μg/kg LPS (E. coli 055, Difco Laboratories, Detroit, MI) were injected i.p.

2.4. Procedure

During the week preceding EAE induction, mice were familiarized with the experimental conditions. Each mouse was provided ad libitum with food pellets and water. Every morning the water tube was replaced by another tube, containing 2% sucrose solution, for 4 h. The food pellets were put on the floor of the cage and the drinking tubes were low enough to enable sick mice to eat and drink effortlessly. In the 3 days preceding the inoculation, body weight and 4 h intake of food and sucrose solution were measured, averaged and considered as baseline level. This measurement period was chosen because during the first 4 h of the dark phase mice complete most of their daily food and liquid consumption. Immediately after the measurement of food and sucrose intake, a conspecific juvenile was placed in each mouse’s home cage for 2 min, and the time spent by the mouse in sniffing the juvenile was measured, averaged and considered as baseline social exploration level. Following the inoculation, mice were observed daily for neurological and behavioral alterations. The day of disease onset was established separately for each mouse. From that day on, mice were assigned into a drug treatment or saline control group. Five separate experiments were conducted with the following treatments: dexamethasone, pentoxifylline, IL-1ra, pentoxifylline and IL-1ra, or indomethacin. Mice were injected at the beginning of the dark phase, and 4 h later food and sucrose intake and social exploration were measured.

In the experiments with LPS-treated mice, baseline measures were collected as in the EAE experiments, except that baseline measures were preceded by saline injections.
On the experiment day, SJL/J or C57Bl/6 (TNFR1+/+ and TNFR1−/−) mice were injected with 50 μg/kg LPS. SJL/J mice were also injected with saline or 100 mg/kg pentoxifylline or 100 mg/kg IL-1ra or 10 mg/kg pentoxifylline + 100 mg/kg IL-1ra i.p. or 10 mg/kg indomethacin s.c. Body weight changes were measured 24 h post injections. Food and sucrose intakes were measured 2 and 24 h post injection. Social exploration was measured 3 h post injection.

2.5. Statistical analysis

Behavioral variables were calculated for each mouse as percent of baseline, by dividing each measured variable by the baseline measure, and multiplying it by 100. Results were analyzed by two-way ANOVAs with EAE/saline as a between-subject factor, and the day as a repeated measures, within-subject factor. Results were further analyzed by planned contrasts and post hoc corrected Student’s t-test. Incidence of disease was analyzed by χ² test.

3. Results

3.1. Effect of dexamethasone on the EBS

The effects of dexamethasone on the neurological score and the EBS were tested during 2 days of treatment (the day of disease onset and the following day). Dexamethasone produced a mild reduction in neurological score, which did not reach statistical significance (F(1,15) = 1.57, p>0.05) (Fig. 1A). EAE-associated decrease in body weight was also not affected by dexamethasone (F(1,15) = 3.18, p>0.05) (Fig. 1B).

EAE was associated with decreased food intake, which was significantly attenuated by the dexamethasone treatment (F(1,15) = 5.26, p<0.05) (Fig. 1C). EAE was also...
associated with a reduction in sucrose consumption and social exploration. These reductions were markedly attenuated in the dexamethasone group during the second day of treatment (Fig. 1D,E), reflected by a significant interaction between dexamethasone/saline injection and the day of injection ($F(1,15) = 4.95$ and $5.5$, for sucrose intake and social exploration, respectively, $p < 0.05$).

To control for a secondary effect of the slight dexamethasone-induced motor improvement on the behavioral measures, a covariance analysis was conducted with the motor improvement, defined as the difference in motor score between the days, as a covariant. The effect of dexamethasone on sucrose consumption and social exploration remained significant ($F(1,15) = 4.52$ and $5.79$, for sucrose intake and social exploration, respectively, $p < 0.05$), indicating motor-independent effect of the treatment on these variables.

### 3.2. Effect of pentoxifylline on the EBS

In two different experiments, EAE was induced and 10 or 100 mg/kg pentoxifylline were injected i.p. daily, starting at disease onset. For the low dose, ANOVA with repeated measures revealed neither a main effect of treatment, nor an interaction between treatment and time on any of the measured variables ($p > 0.05$) (data not shown). Similarly, the high dose of pentoxifylline had no effect on any of the variables measured (Fig. 2A–E), as reflected by ANOVA with repeated measures analysis ($F(1,8) = 0.11$, 0.66, 2.1, 0.69 and $0.16$, $p > 0.05$, for the clinical score, body weight change, food intake, sucrose intake and social exploration, respectively).

### 3.3. Effect of p55 TNF receptor deletion on the EBS

Female wild type and TNFR1$^-/-$ C57Bl/6 mice were immunized with MOG$^{35-55}$. Incidence and date of onset of disease differed significantly between groups. Incidence was 12 out of 12 and 5 out of 19 in the wild type and...
TNFrKO groups, respectively ($\chi^2(1)=116.4, p<0.01$). Further analysis was restricted to the mice that presented clinical symptoms. Average onset of disease occurred on days 14.8 and 30.4 post immunization in the wild type and TNFR−−/−− groups, respectively ($t(15)=6.36, p<0.01$). Clinical symptoms among ill mice were attenuated more rapidly in the TNFR−−/−− group (significant difference beginning 4 days post disease onset), reflected by a significant group by time interaction ($F(8,120)=3.16, p<0.01$). However, body weight loss and reduction in food intake were similar in both groups ($F(11,12)=0.5, 0.2, 2.1, 1.3$ and $1.3, p>0.05$, for clinical score, body weight, food intake, sucrose intake and social exploration, respectively). However, this was mainly due to the mild and short course of the disease in this particular experiment, in which the reduction in the behavioral symptoms were mainly limited to the day of onset of the neurological symptoms. Thus, another statistical analysis of these variables was conducted, restricted to the first day of treatment. IL-1ra had no effect on clinical score and body weight loss ($F(2,22)=0.46$ and $0.19$, respectively, $p>0.05$). In contrast, IL-1ra prevented the decreases in food and sucrose intake associated with EAE ($t(11)=-2.2$ and $-2.1$, respectively, $p<0.05$), but it had no effect on social exploration ($t(11)=0.6, p>0.05$) (Fig. 3C–E).

To confirm the effect of IL-1ra on the EBS, we attempted to replicate the results in another model of EAE. Female C57BI/6 mice with MOG-induced EAE were injected with either 10 or 100 mg/kg IL-1ra, at 8:30 AM (just before the beginning of the behavioral measures) and again at 15:30

3.4. Effect of IL-1ra on the EBS in SJL/J and C57BI/6 mice

In the first experiment, EAE was induced in female SJL/J mice. IL-1ra (100 mg/kg/day) was injected for 3 days, beginning at the onset day of the neurological symptoms. Overall analysis revealed insignificant effects of IL-1ra ($F(2,22)=0.5, 0.2, 2.1, 1.3$ and $1.3, p>0.05$, for clinical score, body weight, food intake, sucrose intake and social exploration, respectively). However, this was mainly due to the mild and short course of the disease in this particular experiment, in which the reduction in the behavioral symptoms were mainly limited to the day of onset of the neurological symptoms. Thus, another statistical analysis of these variables was conducted, restricted to the first day of treatment. IL-1ra had no effect on clinical score and body weight loss ($F(2,22)=0.46$ and $0.19$, respectively, $p>0.05$). In contrast, IL-1ra prevented the decreases in food and sucrose intake associated with EAE ($t(11)=-2.2$ and $-2.1$, respectively, $p<0.05$), but it had no effect on social exploration ($t(11)=0.6, p>0.05$) (Fig. 3C–E).
In each of the four separate experiments, all animals were first injected with saline and baseline measures were taken. Two days later, all animals were injected with LPS (50 mg/kg) and the effect of i.p. injections of 100 mg/kg pentoxifylline, p55 TNFR deletion, 20 mg/kg IL-1ra and 10 mg/kg indomethacin on sickness behavior were compared to saline injections in the four separate experiments. All measures are represented as percent of baseline value. Data represent the mean (±S.E.M.) of 7–10 mice/group.

**Significantly different from the TNFR1+/+ group.

*Significantly different from the saline-injected group.

In the present study, dexamethasone had only mild effect on the clinical score and body weight loss ($F(6,60)=0.63$ and $0.55$, respectively, $p>0.05$) (Fig. 4A,B), but it produced a dose-dependent attenuation of the EAE-associated decrease in food intake ($F(2,29)=2.6$ $p<0.05$) (Fig. 4C). Sucrose intake and social exploration were not influenced by IL-1ra (Fig. 4D,E) ($F(2,23)=0.69$ and 0.6, $p>0.05$, for sucrose intake and social exploration, respectively).

### 3.5. Effect of co-administration of IL-1ra and pentoxifylline on the EBS

Female SJL/J mice with PLP-induced EAE were injected daily with both pentoxifylline and IL-1ra, beginning at the day of the neurological symptoms onset. The treatment had no significant effect on EAE-associated motor impairment and loss of body weight ($F(1,17)=2.5$ and 0.2, respectively, $p>0.05$) (Fig. 5A,B). However, pentoxifylline and IL-1ra treated mice showed significantly less suppression of food consumption, sucrose consumption and social exploration compared to saline-treated mice ($F(1,17)=4.8, 4.9$ and 8.6, $p<0.05$, respectively).

### 3.6. Effect of indomethacin on the EBS

Female SJL/J mice with PLP-induced EAE were injected daily with 10 mg/kg indomethacin, beginning at the day of the neurological symptoms onset. Indomethacin had no significant effect on EAE-associated motor impairment and loss of body weight ($F(1,18)=0.53$ and 1.57, respectively, $p>0.05$) (Fig. 6A,B). However, indomethacin-treated mice showed significantly less suppression of food consumption and social exploration compared to vehicle-treated mice ($F(1,18)=5.23$ and 14.39, $p<0.05$ and 0.01, respectively) and a tendency for increased sucrose consumption ($F(1,18)=2.4, P>0.05$) (Fig. 6C–E).

### 3.7. Effect of pentoxifylline, p55 TNFR deletion, IL-1ra and indomethacin on LPS-induced sickness behavior

In five separate experiments, the effects of the previous treatments were examined on LPS-induced sickness behavior. LPS reliably decreased all behavioral measures. Table 1 summarizes the results of the five experiments, indicating the efficacy of the different treatments to significantly attenuate most of the effects induced by LPS. The effect of pentoxifylline was maximal during the first 2 h post injection; the effects of TNFR targeting and IL-1ra were maintained for the whole measurement period, and the effect of indomethacin was maximal between 2 and 24 h post-injection.

### 4. Discussion

The results of the present study corroborate our previous report that EAE is associated with a behavioral syndrome, consisting of a reduction in food and sucrose intake and in social exploration (Pollak et al., 2000). Furthermore, using pharmacological treatments, we demonstrated here the critical role of inflammatory processes in mediating specific aspects of the EBS. Administration of PGE$_2$ synthesis inhibitor or IL-1ra attenuated the several aspects of the behavioral syndrome. Co-administration of IL-1ra and TNF-α synthesis inhibitor further ameliorated the behavioral syndrome. In contrast, pharmacological synthesis inhibition of TNF-α alone or gene-targeted deletion of one of its receptors did not affect the EBS, indicating that TNF-α activity is not necessary for the induction of the EBS.

In the present study, dexamethasone had only mild (statistically insignificant) effect on EAE-associated clinical score and loss of body weight, and none of the other pharmacological treatments had effect on the clinical score and body weight. These results indicate that motor impair-
ment does not underlie the EBS. However, these findings seem to be inconsistent with several previous studies, which reported that dexamethasone or IL-1ra attenuated disease severity, reflected by lower clinical scores. This discrepancy should be attributed to differences in dosage and timing. For instance, in our experiments dexamethasone and IL-1ra treatments commenced on the day of clinical disease onset and were given for only 2–3 days, whereas in most of the studies that reported beneficial effect, the compounds were injected chronically, beginning before disease onset (Matous-Malbohan et al., 1976; Martin and Nearn, 1995; Badovinac et al., 1998). It is likely that if the experiments had been continued for several more days, dexamethasone, and possibly other treatments, would have been effective. However, at those time points the EBS is already fully recovered.

We have recently reported that IL-1 and TNF-α gene expression correlate in time with the behavioral syndrome of EAE (Pollak et al., in this issue). The effect of IL-1ra in the present study is consistent with the finding that IL-1 production increases from the onset to the peak of the EBS, and declines along the recovery of this syndrome. The lack of influence of TNF-α activity inhibitors indicates that although its production coincides with the full-blown behavioral syndrome, TNF-α has no obligatorily causative role in mediating the behavioral alterations. High levels of PGE2 accompany EAE, but show no temporal correlation with the behavioral alterations. Together with the present findings, it may be suggested that PGE2 is necessary, but not sufficient, for the induction of EBS. This latter conclusion is consistent with other studies, reporting that PGE2 administration did not reduce food intake (Konturek et al., 1999).

Consistent with the findings from other laboratories, p55 TNF receptor knockout mice were less susceptible to EAE and showed delayed onset of the disease (Eugster et al., 1999; Schiffler and Dunn, 2000). However, TNFR1−/− mice with EAE showed sickness behavior that was similar in magnitude to that in TNFR1+/+ mice. Interestingly, Eugster et al. report that EAE in TNFR1−/− mice was associated with reduced demyelination, but with profound inflammation. Taken together, these findings suggest that inflammation is associated with the behavioral alterations, and that TNFR1 is essential neither for the induction of inflammation, nor for the establishment of the behavioral symptoms.

In spite of very small homology between IL-1 and TNF-α, and the fact that they bind to different receptors, these two cytokines share many biological properties. For instance, both stimulate PGE2 production and releases of platelet-activating factor, both are endogenous pyrogens through direct effect on the hypothalamic thermoregulatory center, and both are implicated in the pathogenesis of several diseases including EAE (Dinarello, 1999). In the present study, LPS-induced sickness behavior was attenuated by administration of either IL-1ra or pentoxifylline, whereas the EBS was not attenuated at all by pentoxifylline, mildly attenuated by IL-1ra, and was reversed by co-administration of the two compounds. These results, together with previous studies on the effect of pharmacological and genetic treatments, indicate that the relative role played by the two cytokines in sickness behavior depends on the specific model. In some models, blockade of either IL-1 or TNF-α attenuated illness-associated sickness behavior, suggesting that in these models each of these cytokines is independently involved in the mediation of the behavioral syndrome. For example, in the present study, administration of either IL-1ra or pentoxifylline attenuated sickness behavior in LPS-injected mice. Similar findings were reported with influenza-induced sickness behavior (Swiergiel and Dunn, 1999). In other studies, the effect of IL-1 and TNF-α seem to be complimentary. For example, administration of either IL-1ra or pentoxifylline by itself had no effect on M. fermentans-induced sickness behavior, whereas simultaneous administration of both blockers significantly attenuated components of sickness behavior (Yirmiya et al., 1999a). Similarly, IL-1 receptor knockout mice showed normal LPS-induced sickness behavior; however, in these mice (but not in the wild-type mice), blocking TNF-α by its binding protein attenuated sickness behavior (Bluthe et al., 2000). In another disease model, the behavioral effects of HIV gp120 were attenuated by IL-1, but not TNF-α inhibitors (Barak et al., 2002).

In the present study, inhibitors of IL-1, TNF-α and PGE2 activity were found to attenuate LPS-induced sickness behavior. Interestingly, the ameliorative effect of pentoxifylline was limited to the first 2 h post LPS injections, whereas the main effect of indomethacin began only 2 h after LPS administration. This finding raises the possibility that different mechanisms mediate the behavioral alterations along the course of the sickness. Alternatively, the temporal differences in effectiveness are due to the different routes that were used for the injections, i.e., i.p. (for pentoxifylline) vs. s.c. (for indomethacin).

Using the LPS and IL-1 models, both peripheral and central mechanisms of sickness behavior were uncovered (Dantzer, 1999; Dantzer, 2001). In the present study, we did not address the location in which inflammatory mediators produce their effects on the EBS, using treatments that affect inflammatory mediators both in the periphery and the brain. Dexamethasone does not readily cross the blood–brain barrier (BBB) (Meijer et al., 1998); however, peripheral administration of this drug strongly reduces brain inflammation, pro-inflammatory cytokines expression, PGE2 production and microglial activation (Weidenfeld et al., 1988; Sacco et al., 1998; Schlesener et al., 1999; Paul et al., 2000). In contrast, when administered peripherally, indomethacin is readily available to brain cells by penetration of the BBB (Bannwarth et al., 1989). In addition, peripheral administration of indomethacin or pentoxifylline blocks the central synthesis of PGE2 or TNF-α, respectively (Shohami et al., 1997; Yirmiya et al., 1997). IL-1ra cannot penetrate the BBB by diffusion, but it is transported across that interface by a saturable system (Gutierrez
et al., 1994). According to Gutierrez et al., about 0.5% of the dose injected i.v. enters each gram of the brain via this system. This estimation suggests that about 10–15% of the dose injected i.v. enters each gram of the brain via this system. The behavioral syndrome that accompanies the mouse model resembles some of the features of MS-associated depression (Pollak et al., 2002). Elucidating the mechanisms that underlie the EBS may provide insights to the mechanisms of the emotional, behavioral and cognitive alterations in MS patients. For example, we are currently planning to examine whether the steroid anti-inflammatory treatment has marked effects on mood and behavioral symptoms in MS patients during exacerbations. Such studies may result in better preventive and therapeutic procedures for MS-associated neuropsychiatric disturbances.

Acknowledgements

The authors thank Orli Bar-Shalev, Shira Gur, Lior Friedman, Yael Perets, Meital Shahar, Michal Shlayer, Michal Shuker, and Gili Wolf for their excellent help in running the experiments. The research was supported by a grant from the Israel Science Foundation (No. 820/00) and in part by the Lena P. Harvey Endowment Fund for Neurological Research. RY is a member of the Eric Roland Center for Neurodegenerative Diseases at the Hebrew University of Jerusalem.

References


Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Pollmächer, T., 2001. Endotoxin-induced emotional and cognitive disturbances in...
healthy volunteers are associated with increased plasma levels of cytokines and cortisol. Arch. Gen. Psychiatry 58, 445–452.


