The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines

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Abstract

Antidepressants are known to impact on the immune system. In this study, we examined the immunomodulatory properties of venlafaxine, a selective serotonin/norepinephrine reuptake inhibitor (SNRI), in murine experimental autoimmune encephalomyelitis (EAE), a T-cell-mediated CNS demyelinating disease model of multiple sclerosis. EAE was induced in SJL/J mice by adoptive transfer of myelin-specific T cells. Mice received different doses of venlafaxine before induction and after onset of disease. Sustained daily oral treatment with 6, 20 and 60 mg/kg significantly ameliorated the clinical symptoms of the disease compared to vehicle during both preventive and therapeutic intervention. Venlafaxine suppressed the generation of pro-inflammatory cytokines IL-12 p40, TNF-α and IFN-γ in encephalitogenic T-cell clones, splenocytes and peritoneal macrophages in vitro. It also diminished mRNA expression of a number of inflammatory genes in the inflamed CNS tissue, among them CD3, CD8, Granzyme B, IL-12 p40, IFN-γ, TNF-α and the chemokines Ccl2 and RANTES, whereas the expression of brain-derived neurotrophic factor was increased. These findings demonstrate the strong immunomodulatory property of the selective SNRI venlafaxine. Further studies are warranted to clarify whether venlafaxine may exert similar effects in humans.

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Key words: Antidepressant, cytokines, EAE, multiple sclerosis, venlafaxine.

Introduction

Venlafaxine, a selective serotonin/norepinephrine reuptake inhibitor (SNRI), is a drug frequently used for the treatment of affective disorders. Besides its efficacy in the therapy of major depression a number of studies have suggested immunomodulatory effects of venlafaxine in vitro similar to those that have been demonstrated for other antidepressants such as fluoxetine, imipramine or amitryptiline (e.g. Maes, 2001; Obuchowicz et al., 2006). Venlafaxine has been shown to down-regulate interferon-γ (IFN-γ) production in whole-blood cells from patients with treatment-resistant depression while up-regulating anti-inflammatory cytokines such as interleukin-10 (IL-10) (Kubera et al., 2001). Furthermore, venlafaxine reduces the secretion of the pro-inflammatory cytokines interleukin-6 (IL-6) and IFN-γ from astrocytes and changes the phenotype of primary microglia from activated to resting morphology (Vollmar et al., 2008).

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) of unknown aetiology. While a number of pro-inflammatory cytokines [e.g. IL-17, IFN-γ, tumour necrosis factor-α (TNF-α)] have been found in the cerebrospinal fluid (Ishizu et al., 2005) or in lesions during acute MS relapses (Lassmann et al., 2007), anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) (Carrieri et al., 1998)
have been detected during remission, suggesting an imbalance of pro- and anti-inflammatory cytokines in this disorder. Besides neurological deficits, fatigue and depressive episodes appear in the course of this disease in more than 50% of MS patients (Joffe, 2005).

Experimental autoimmune encephalomyelitis (EAE) is the well-known animal model for MS which allows the study of inflammation-related damage of CNS tissue. EAE can be induced in several animal strains by immunization with myelin components or by adoptive transfer of myelin-specific T cells (Gold et al., 2006; ’t Hart and Amor, 2003; Zamvil and Steinman, 1990). The disease is clinically characterized by neurological deficits, mainly paresis, and histopathologically by perivascular infiltrates in the CNS. In most EAE models the disease is initiated by CD4+, MHC class II-restricted Th1 and Th17 cells (Stromnes et al., 2008). Activated CD4+ T cells can cross the blood–brain barrier (BBB), infiltrate the CNS and secrete chemokines and pro-inflammatory cytokines upon re-challenge by microglial cells and autoantigen. The secreted chemokines and cytokines will attract monocytes to the lesion and activate microglial cells which both significantly contribute to CNS tissue damage by secreting neurotoxic molecules. Furthermore, astroglial cells proliferate within demyelinating lesions of MS and EAE (Holley et al., 2003; Tani et al., 1996) and promote inflammation, oligodendrocyte damage and glial scarring (Ambrosini et al., 2005).

In-vivo findings on the clinical course of experimental autoimmune models demonstrate a significant impact of neurotransmitter reuptake modulation. 5-HT transporter-deficient mice develop less severe EAE with reduced infiltration of the CNS compared to wild-type animals (Hofstetter et al., 2005). Clinical signs of experimental allergic neuritis are less severe in 5-HT reuptake inhibitor-treated animals (Bengtsson et al., 1992). Further, the selective phosphodiesterase type-4 inhibitor rolipram which exerts antidepressant properties suppresses clinical and histological signs of EAE (SOMMER et al., 1995). Recently, hyperforin was found to have suppressive effects on EAE by down-regulating effector functions of activated T cells (Cabrelle et al., 2008).

Thus far, modern antidepressants especially selective SNRIs have not been investigated for their impact on CNS autoimmunity in vivo.

In this study, we report that venlafaxine efficiently suppresses EAE clinically and histopathologically. In-vitro and in-vivo data suggest that this effect is mediated by the strong anti-inflammatory activity of venlafaxine.

Methods

Animals and induction of EAE

Female SJL/J mice were obtained from Harlan Winkelmann (Borchen, Germany). They were kept according to the regional animal guidelines and used from age 6–12 wk. All procedures were performed according to the local guidelines and the study was approved by the regional Animal Care Committee.

EAE was induced by the adoptive transfer of 5 × 10⁶ to 2 × 10⁷ cells i.p. into syngenic recipients according to previously published protocols (Nessler et al., 2006; Stromnes and Goverman, 2006). Briefly, SJL/J mice were subcutaneously immunized with 200 μg/animal proteolipid protein (PLP) 139–151 (HSLGKWLGH-PDKF, single-letter code, Jerini, Berlin) emulsified in incomplete Freund’s adjuvant (Sigma-Aldrich, Munich, Germany) supplemented with 5 mg/ml inactivated M. tuberculosis H37RA (Difco Laboratories, Detroit, MI, USA). The draining lymph nodes were removed 11 d later and single-cell suspensions were made. After in-vitro restimulation with 10 μg/ml PLP 139–151 for 4 d, 5 × 10⁶ to 2 × 10⁷ cells were injected intraperitoneally into syngenic recipients.

Clinical signs of EAE were ranked from 0 (normal), 1 (tail limpness), 2 (paraparesis with clumsy gait), 3 (hindlimb paralysis), 4 (hind- and forelimb paralysis), 5 (death) according to Kassiotis et al. (1999). All ratings were done by observers blinded to the treatment.

Venlafaxine treatment

Mice were treated daily with 6, 20 or 60 mg/kg venlafaxine p.o. (the substance was kindly provided by Wyeth Pharma, Münster, Germany) in 100 μl PBS starting at the day of induction or after the onset of clinical symptoms. Control mice received PBS alone. In another experiment, osmotic pumps (Alzet model 2002; Alzet, Palo Alto, CA, USA) were implanted subcutaneously 2 d prior to disease induction and vehicle or 60 mg/kg/d venlafaxine were continuously administered for 14 d.

Histology and immunohistochemistry

Mice were perfused with PBS and 4% paraformaldehyde intracardially. Brains and spinal cords were dissected and embedded in paraffin. Inflammation was assessed by haematoxylin staining (Nessler et al., 2007). The extent of inflammation is expressed as the mean number of inflammatory infiltrates per spinal cord cross-section (inflammatory index). A minimum of 10 spinal cord cross-sections per animal were examined.
Immunohistochemistry was performed with an antibody against the glial fibrillary acidic protein (GFAP, clone 6F2, Dako North America, Carpinteria, CA, USA) as described previously (Abdul-Majid et al., 2003). Tissues were pretreated with micro-waving in 10 mM citrate buffer (pH 6.0) twice for 5 min. Bound antibody was visualized using an avidin-biotin technique (extravidin-peroxidase, Sigma-Aldrich). DAB chromogen (Dako) was applied for 25 min and the slides were counterstained with haematoxylin. Control sections were incubated in the absence of primary antibody or with non-immune sera. Slides were counterstained with haematoxylin and coverslipped.

Histological analyses were performed on spinal cord sections derived from the prevention experiment (Figure 1a).

Cell culture

Cell culture was performed in RPMI 1640 medium containing 10% fetal calf serum, non-essential amino acids, Hepes, l-glutamine, 2-mercaptoethanol and antibiotics (Sommer et al., 1997). The cells were cultivated at 37 °C in a humidified incubator at 5% CO₂.

Cytokine production

In-vitro effects of venlafaxine were studied on the myelin–oligodendrocyte–glycoprotein (MOG) 35-55
specific encephalitogenic T-cell clone 5–8 (S. Nessler et al., unpublished observations), on PLP 139–51 specific splenocytes and on peritoneal macrophages activated with lipopolysaccharides (LPS).

T-cell clone 5–8 was restimulated with 10 μg/ml MOG 35–55 (MEGVWYRSPFSRVLHYRNGK, single-letter code, Jerini, Berlin) and 4 x 10⁶/ml irradiated antigen presenting cells (APC) for 48 h. Venlafaxine (titrated from 10⁻⁵ to 10⁻¹⁰ mol/l) was added at the time of restimulation. Supernatants were collected after 48 h and kept at −80 °C for further analysis by cytokine- and chemokine-specific ELISAs. Spleens from animals actively immunized with PLP 139–151 were removed at day 11 and single-cell suspensions were generated. These cells were restimulated with 10 μg/ml PLP in the presence of 10⁻⁴ to 10⁻¹⁸ mol/l venlafaxine and supernatants were removed after 48 h and processed as described above.

Finally, primary macrophages were isolated from the peritoneal cavity of mice 3 d after intraperitoneal injection with 3 ml of 3% (w/v) thioglycollate (BD Diagnostics Systems, Sparks, MD, USA) according to previously published protocols (Ousman et al., 2007). These cells were cultured with media alone for 48 h and then activated with 100 ng/ml LPS (Sigma-Aldrich) in the presence of 900 nM and 250 nM, respectively. PCR reactions were prepared in a final volume of 20 μl, with final concentrations of 1 x TaqMan Universal Fast PCR Mastermix (Applied Biosystems) and cDNA derived from 20 ng of input RNA as determined by full-spectrum UV/Vis spectrophotometric measurements (Nanodrop, Peqlab; Erlangen, Germany). Thermal cycling conditions comprised DNA polymerase activation at 95 °C for 2 min, 40 cycles of denaturation at 95 °C for 3 s, and annealing and extension at 60 °C for 30 s. Each measurement was performed in duplicate and the threshold cycle was determined. The following gene expression assays have been used (Applied Biosystems): BDNF (Mm00432069_m1), Ccl2 (Mm99999056_m1), CD3 (Mm00599683_m1), CD8 (Mmm01182107_g1), Granzyme B (Mm00442834_m1), IFN-γ (Mm00801778_m1), IL-6 (Mm00444165_m1), IL-12 p40 (Mm00432069_m1), TNF-α (Mm00443258_m1), RANTES (Mm01302488_m1).

Expression levels for each gene of interest were calculated by normalizing the quantified mRNA amount to GAPDH. Relative gene expression was determined and used to test significance between treatment and control groups.

Data analysis

Data are presented as mean ± standard error of the mean (s.e.m.). Statistical comparisons between EAE treatment groups were performed by the two-tailed Kruskal–Wallis test. Unpaired t tests were used for mRNA expression data and histopathological scores. Values of p < 0.05 were considered significant. Graphs were generated using GraphPad Prism software (San Diego, CA, USA).

Results

Venlafaxine treatment ameliorates clinical signs of EAE

Treatment with venlafaxine significantly ameliorated EAE when treatment was initiated at the day of disease...
induction (see Figure 1a and Table 1 for means, standard errors and statistical comparisons with the Kruskal–Wallis test). Early oral venlafaxine treatment was effective at 6, 20 and 60 mg/kg. Whereas all animals in the PBS-treated control group developed signs of EAE the disease incidence in the treatment groups was only 50%. Moreover, disease severity was milder in the affected animals in the treatment groups compared to the control group.

When animals were treated using venlafaxine with osmotic pumps exclusively during the induction phase, EAE symptoms were delayed and less pronounced in the treatment than in the control group (Figure 1b). However, sustained administration of venlafaxine was clearly more efficient than the 2-wk pretreatment.

Therapeutic intervention with venlafaxine at the beginning of EAE symptoms (Figure 1c) showed a dose–response relationship with a significant reduction of EAE symptoms at 60 mg/kg venlafaxine compared to vehicle-treated animals. If venlafaxine treatment was started after manifestation of severe symptoms (Figure 1d) significant amelioration of EAE symptoms could be demonstrated for 20 mg/kg and 60 mg/kg venlafaxine after 2 wk therapy.

**Venlafaxine treatment reduces the number of inflammatory infiltrates and prevents gliosis in EAE lesions**

Histology of control mice with clinical signs of EAE after adoptive transfer of PLP-specific cells revealed dense subpial and perivascular infiltrates expanding to the parenchyma (Figure 2b). Venlafaxine-treated mice showed markedly reduced CNS inflammation and were largely devoid of inflammatory infiltrates in the brain and spinal cord (Figure 2a). The average number of inflammatory infiltrates per spinal cord cross-section (inflammatory index, Figure 2f) was 6.78 ± 0.73 in untreated animals compared to 2.03 ± 0.73 in the 6 mg/kg group ($t = 4.56, p < 0.0018$ revealed by unpaired $t$ test) and 0.99 ± 0.42 in the 60 mg/kg group ($t = 6.81, p = 0.0001$).

In untreated mice (Figure 2d), severe astrogliosis in the parenchyma was observed in the chronic disease phase, whereas treated mice (Figure 2c) showed no

### Table 1. Summary of the effects of venlafaxine pretreatment and active treatment on the cumulative score, maximum disease score and disease incidence

<table>
<thead>
<tr>
<th></th>
<th>Adoptive transfer experimental autoimmune encephalomyelitis in SJL/J mice</th>
<th></th>
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<tr>
<td></td>
<td>Pretreatment Mean (S.E.M.)</td>
<td>Pump treatment Mean (S.E.M.)</td>
<td>Active treatment Mean (S.E.M.)</td>
<td>Mean (S.E.M.)</td>
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<tr>
<td>Cumulative score</td>
<td></td>
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<tr>
<td>Vehicle</td>
<td>26.78 (1.82)</td>
<td>187.18 (16.75)</td>
<td>106.95 (7.21)</td>
<td>60.73 (3.70)</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>7.72 (3.19)*</td>
<td>n.a.</td>
<td>78.25 (14.75)</td>
<td>n.a.</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>6.31 (2.40)**</td>
<td>n.a.</td>
<td>n.a.</td>
<td>51.47 (4.83)</td>
</tr>
<tr>
<td>60 mg/kg</td>
<td>6.03 (2.02)*</td>
<td>96.26 (32.65)*</td>
<td>45.63 (13.23)**</td>
<td>46.43 (4.02)*</td>
</tr>
<tr>
<td>Maximum score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>2.4 (0.1)</td>
<td>3.75 (0.14)</td>
<td>3.88 (0.15)</td>
<td>3.95 (0.21)</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>1.19 (0.35)**</td>
<td>n.a.</td>
<td>3.15 (0.36)</td>
<td>n.a.</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>1.09 (0.34)**</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3.6 (0.266)</td>
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<tr>
<td>60 mg/kg</td>
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<td>2.89 (0.48)</td>
<td>2.35 (0.33)*</td>
<td>3.3 (0.25)</td>
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<tr>
<td>Disease incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
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<td>7/7</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>4/8</td>
<td>n.a.</td>
<td>10/10</td>
<td>n.a.</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>4/8</td>
<td>n.a.</td>
<td>10/10</td>
<td>10/10</td>
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<tr>
<td>60 mg/kg</td>
<td>4/8</td>
<td>6/7</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Animals per group</td>
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<td>n = 7</td>
<td>n = 10</td>
<td>n = 10</td>
</tr>
<tr>
<td>Treatment period</td>
<td>25 d</td>
<td>14 d</td>
<td>40 d</td>
<td>20 d</td>
</tr>
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</table>

Significant differences between venlafaxine-treated and vehicle-treated mice were assessed by two-tailed Kruskal–Wallis test. *$p < 0.05$, **$p < 0.01$. 
Figure 2. Venlafaxine reduces the histopathological manifestation of experimental autoimmune encephalomyelitis. (a) Shows a representative haematoxylin staining (40× original magnification) of the thoracic spinal cord from a venlafaxine-treated animal (20 mg/kg, d) without inflammatory foci after 3 wk of adoptive transfer. (b) Illustrates a spinal cord section of a vehicle-treated mouse with considerable amounts of inflammatory foci [(e) 200× magnification], with dense mononuclear cell infiltration around the meninges. Arrows indicate mononuclear cell infiltrates. (f) Shows the mean numbers of inflammatory infiltrates per spinal cord cross-section (inflammatory index). A minimum of 10 spinal cord cross-sections per animal were examined. Statistical difference was assessed by unpaired, two-tailed $t$ test. Panels (c) and (d) illustrate reactive gliosis to inflammation in the brainstems of representative untreated [(d) 200× magnification] and treated (c) animals as revealed by GFAP immunostaining and haematoxylin counterstaining after 2 wk of disease onset. In untreated mice [(d) 200× magnification], inflammatory cell infiltration evokes severe astrogliosis in the parenchyma whereas treated mice are almost free of reactive gliosis. Data were confirmed (g) by quantitative GFAP gene expression analysis performed in mice receiving different doses of venlafaxine as preventive treatment. Statistical evaluation of relative GFAP gene expression was assessed by two-tailed Mann–Whitney $U$ test (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Figure 3. Venlafaxine reduces the mRNA expression in spinal cord tissue of EAE mice at day 48 after disease induction. Here, the quantitative mRNA expression of inflammation-related genes in the spinal cord tissue of venlafaxine- and vehicle-treated mice is illustrated. Gene expression analysis was performed on tissue from one therapeutic trial (Figure 1c). The GAPDH-normalized relative gene expression ($\Delta\Delta CT$) is shown for single animals. Both doses of venlafaxine suppressed the in-vivo expression of the CD3 T cells, cytotoxic CD8 T cells and Granzyme B genes. However, the effect was more pronounced under high-dose treatment. Further, the antidepressant significantly reduced the gene expression of the pro-inflammatory cytokines, IL-12 p40, IFN-γ and TNF-α and the chemokines Ccl2 and Ccl5 whereas the expression of brain-derived neurotrophic factor (BDNF) was significantly increased. The $n$-fold change in mRNA expression compared to control group is summarized for each inflammation-related gene. Statistical difference was assessed by unpaired, two-tailed $t$ test (* $p<0.05$, ** $p<0.01$).
Figure 3. For legend see opposite page.
reactive gliosis as revealed by GFAP immunostaining. Data were confirmed by GFAP gene expression studies. GFAP gene expression was significantly higher in untreated mice compared to venlafaxine-treated mice.

**Decreased expression of pro-inflammatory gene transcripts in EAE lesions during venlafaxine treatment**

In line with the histopathological studies, treatment with venlafaxine reduced the expression of T-cell genes (CD3 and CD8) in inflamed spinal cord tissue (Figure 3). The effect was dose dependent and reached the highest suppressive effect at 60 mg/kg/d. Further, Granzyme B, a gene expressed by cytotoxic CD8 T cells and natural killer cells, was reduced in animals receiving high doses of venlafaxine. The drug also had a significant impact on IL-12 p40, TNF-α and IFN-γ, three pro-inflammatory cytokines produced by macrophages and T cells respectively. Moreover, gene transcripts of the chemokines Ccl2 and Ccl5 were strongly reduced in the lesions of treated animals. By contrast, brain-derived neurotrophic factor (BDNF) mRNA expression was significantly up-regulated in the inflamed spinal cord of EAE mice receiving a high dose venlafaxine.

**Venlafaxine reduces the secretion of pro-inflammatory cytokines by T cells and macrophages in vitro**

In vitro, venlafaxine reduced the release of pro-inflammatory cytokines in PLP-specific T cells and MOG 35–55 specific T-cell clones (Figure 4a, b). The effect was most pronounced for IFN-γ and IL-12 p40 with an overall reduction of cytokine secretion by 50%. Venlafaxine also reduced the expression levels of Ccl5, IL-6 and TNF-α in a dose-dependent manner. Peritoneal macrophages released less of the pro-inflammatory cytokines IL-6 and TNF-α upon challenge with venlafaxine (Figure 4c). The suppression of cytokine and chemokine secretions by venlafaxine was dose-dependent and observed at concentrations non-toxic to the cells as assessed by 7-AAD staining (data not shown). Toxicity was only observed when the concentration of venlafaxine exceeded 10⁻³ mol/l.

**Discussion**

In the present study, we have demonstrated that the selective SNRI venlafaxine can suppress the clinical and histopathological signs of EAE. Venlafaxine treatment ameliorates EAE even after disease has been established. Clinical and histopathological treatment effects of venlafaxine have been confirmed by significant and dose-dependent reductions of in-vivo mRNA expression levels of pro-inflammatory cytokines and immune cell markers in the inflamed CNS tissue.

First, gene expression data illustrate the anti-inflammatory properties of venlafaxine in autoimmune CNS diseases applying a method which is characterized by high sensitivity and objective quantifiability in the absence of any in-vitro manipulation. Second, gene expression data were confirmed by immune assays on the protein level. The in-vitro administration of venlafaxine suppressed cytokine production in (i) myelin-specific T cells, (ii) in T-cell clones with high encephalitogenicity and (iii) peritoneal macrophages at low doses, accounting for the immunosuppressive effects.

Venlafaxine strongly reduced the in-vivo gene expression and in-vitro secretion of IL-12 p40 which is considered essential in T-cell-mediated autoimmune diseases (Gran et al., 2004). This is based on the strong capacity of IL-12 to induce T-cell activation, Th1 cytokine differentiation and macrophage activation (Trinchieri and Scott, 1995).

The results of the present study are consistent with in-vitro findings on the anti-inflammatory effects of venlafaxine on primary astroglia and microglia (Kubera et al., 2001; Vollmar et al., 2008). Antidepressants impact on microglial cells by suppression of inflammation-induced cytokine production. Hashioka et al. (2007) showed for several substances (imipramine, fluvoxamine and reboxetine) reduced IL-6 and nitric oxide production after IFN-γ activation. Similar effects were found for amitryptiline in mixed glial and microglial cultures (Obuchowicz et al., 2006).

The mechanisms leading to the reduction of cytokine secretion are still unknown. One putative mechanism (Hindmarch, 2001) is the increase of transcription factors such as intracellular cyclic adenosyl monophosphate (cAMP) resulting in activation of neuroprotective proteins, such as BDNF (Xia et al., 1996), which was also up-regulated in the spinal cord of venlafaxine-treated animals in our study. Other in-vitro studies found antidepressant mediated reduction of cytokine-induced prostaglandin E2 and nitric oxide production by inflammatory cells from synovial tissue (Yaron et al., 1999).

Animals in the present study were treated by oral administration of venlafaxine and by the use of osmotic pumps. Mice treated with 5 mg/kg/d venlafaxine subcutaneously exhibited plasma concentrations of 178.4 ng/ml according to a study by Uhr et al. (2003). Plasma concentrations of venlafaxine up to 600–900 ng/ml have been reported in patients.
chronically treated with 200–300 mg/d venlafaxine (Ilett et al., 2002). Assuming a linear dose–response relation, the applied 6 mg/kg/d and 20 mg/kg/d venlafaxine represent clinically relevant dosages. Oral administration of the drug was clearly superior to the continuous drug administration by osmotic pumps, suggesting that high plasma peaks are beneficial for the therapeutic efficacy of venlafaxine in our model.

At first view, affective disorders and autoimmune diseases such as MS or EAE are completely different diseases with distinct clinical phenotypes. However, the incidence of neuropsychiatric disorders among MS patients is remarkably high (Cetin et al., 2007; Ghaffar and Feinstein, 2007) and introduces a new perspective on the interaction of both diseases. Interestingly, a study by Mohr et al. (2001) found that MS patients with concomitant depression revealed a reduction of MOG-stimulated IFN-γ production under antidepressant therapy with sertraline and cognitive therapy. Even in EAE, Pollak et al. (2002) identified an ‘EAE-associated behavioural syndrome’ which is closely related to human major depression in terms of body weight reduction, changes in food and sucrose intake and a decrease in social exploration.

In the pathogenesis of mood disorders, the role of cytokines has attracted considerable interest during the last decade (e.g. Besedovsky and Rey, 2007). Studies found increased levels of IL-6, IL-1β and TNF-α in stimulated peripheral blood mononuclear cells of depressed patients (Cryanowski et al., 2007). There is growing evidence that the increase in cytokine concentrations accounts for ‘sickness behaviour’ and
depression (e.g. Irwin and Miller, 2007). Antidepressant treatment seems to have suppressing effects on cytokine secretion (Castanon et al., 2002) revealing a fundamental consequence of selective monoaminergic reuptake inhibition.

Interestingly, studies of antidepressant effects of a cyclooxygenase-2 (COX-2) inhibitor (Muller et al., 2006) which curtails prostaglandin E2 generation and the production of pro-inflammatory cytokines showed significant improvement in depressive patients under celecoxib add-on therapy. Further, the same COX-2 inhibitor has been found to have preventive effects in EAE through the suppression of pro-inflammatory cytokine secretion (Miyamoto et al., 2006). COX-2 inhibitors reduce the secretion of IL-12 (Muthian et al., 2006) revealing a mechanism of immunomodulation similar to the one we identified here for venlafaxine. These findings provide further evidence for a neuro-immune interaction and an inflammation-related pathogenesis of affective disorders.

In summary, the clinical effects of venlafaxine on CNS inflammation are marked and warrant replication in human trials to prove efficacy in MS patients.

Note
Supplementary material accompanies this paper on the Journal’s website (http://journals.cambridge.org).

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Statement of Interest
None.

References


