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In Vivo and In Vitro Effects of Glucocorticoids on Lymphocyte Proliferation in Depression

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Summary. Twelve severely depressed patients and 13 healthy controls were studied under baseline, metyrapone and metyrapone plus dexamethasone pretreated conditions. Lymphocyte proliferation data were obtained by concanavalin A, phytohaemagglutinin and pokeweed mitogen (PWM) stimulation. There was a decrease in PWM-induced B-cell proliferation and an increase in inhibition of spontaneous leucocyte proliferation by dexamethasone added in vitro following metyrapone administration in vivo, in healthy controls, which was not present in the depressed patients. These data support the concept of a decreased functional plasticity of the glucocorticoid receptor in depression also at the cellular level.

Key words: Leucocyte proliferation – Glucocorticoids – Depression – Immunity

Introduction

Recent interest has focused on the neuroendocrine-immune interaction in affective disorders. A variety of studies have investigated lymphocyte subsets (Schleifer et al. 1989), natural killer cell activity (Irwin et al. 1988; Schleifer et al. 1989), and the mitogen response to various lectins (Kronfol et al. 1983; Schleifer et al. 1984, 1985; Cosyns et al. 1989). Although initial studies reported a decreased mitogen-induced leucocyte proliferation in depressed patients (Kronfol et al. 1983; Schleifer et al. 1984), this could not be consistently reproduced in later investigations (Schleifer et al. 1985). Instead, other variables, such as age and severity of depression, seemed to play a key role for the lectin-induced blastogenesis (Schleifer et al. 1989).

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Depressed patients exhibit a quite remarkable hypercotisolaemia during depressive illness (Linkowski et al. 1985, 1987) and several lines of evidence suggest an important link between the hypothalamic-pituitary-adrenal axis (HPA) and the immune system (Fauci and Dale 1974; Cupps and Fauci 1982). Glucocorticoids have been shown to inhibit interleukin-1 (IL-1) (Snyder and Unanue 1982) and IL-2 production with subsequently impaired lection-induced blastogenesis (Gillis et al. 1979; Cupps and Fauci 1982). Moreover, depletion of glucocorticoids by metyrapone (MET) resulted in a decrease in pokeweed mitogen (PWM)-induced leucocyte proliferation in normal volunteers, which was reversed by dexamethasone (DEX) administration (Rupprecht et al., submitted).

As human lymphocytes contain glucocorticoid receptors (GRs) (Lippman and Barr 1977; Schlechte et al. 1982; Junker 1983), the present study was designed to explore the effects of depletion of endogenous glucocorticoids by MET and subsequent replacement by DEX in vivo on lymphocyte proliferation characteristics in vitro in depressed patients, when compared with healthy subjects, as a functional probe for the glucocorticoid receptor in depression.

Subjects and Methods

Subjects

Three male and nine female subjects with unipolar major depressive disorder or bipolar depression aged between 18 and 66 years (mean ± SD, 48.7 ± 15.1 years) with a mean (± SD) body weight of 72.5 ± 13.4 kg and three male and ten female healthy controls aged between 33 and 57 years (mean ± SD, 47.6 ± 6.2 years) with a mean (± SD) body weight of 69.2 ± 8.6 kg were studied. All subjects were carefully screened for any medical illness

Table 1. Demographic data, antidepressants applied prior to the washout period and diagnostic description of the depressed patients

Patient no.	Age (years)	Sex	DSM-III-R	HRS-D	Drug-free period (days)	Treatment before drug-free period	Depressive episodes
1	44	F	Bipolar disorder, depressed	33	>28		3
2	66	F	MDD, recurrent, with melancholia	36	>28		2
3	61	F	MDD, recurrent, with melancholia, mood congruent psychotic	28	>28		3
4	64	F	MDD, recurrent, with melancholia	28	>28		4
5	39	F	MDD, recurrent	25	7	Amitriptyline 100 mg	3
6	60	M	MDD, recurrent, with melancholia	24	5	Amitriptyline 100 mg	3
7	60	M	MDD, recurrent, with melancholia	28	5	Maprotiline 150 mg	3
8	34	F	MDD, recurrent, with melancholia	28	4	Maprotiline 100 mg	3
9	54	F	Bipolar disorder, depressed	33	>28		6
10	18	F	MDD, single episode	26	>28		1
11	53	M	MDD, recurrent	26	>21		2
12	34	F	MDD, recurrent	39	5	Amitriptyline 150 mg	3

MDD, Major depressive disorder

that might influence pituitary-adrenal function by medical history, physical examination and routine laboratory tests. Four female depressives and four female controls were tested during the midluteal phase of the cycle; the other females were postmenopausal.

DSM-III-R (American Psychiatric Association 1987) diagnoses were made on all patients by the consensus of two psychiatrists, who were blind to laboratory results. Severity of depression was assessed by the 21-item Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960). The mean (± SD) HRS-D score of the patients was 29.5 ± 4.7, ranging from 24 to 39. Patients were studied after a drug-free period of at least 72 h. Details of clinical and demographic data of the patients and the medication given before the drug-free interval are shown in Table 1.

Controls had no history of psychiatric disorder and were medication free for at least 4 weeks.

Study design

After the nature of the study had been fully explained, written informed consent was obtained from patients and controls. The test protocol was approved by the ethical committee of the University of Würzburg and the requirements of the revised version of the Helsinki Declaration were strictly adhered to. All subjects were admitted to a sleep laboratory unit at least 1 h prior to drug administration or blood sampling.

For determination of lymphocyte proliferation parameters, glucocorticoid binding characteristics, and hormone data, 50 ml blood was collected at 4 p.m. into prechilled plastic tubes containing ethylenediaminetetraacetic acid (EDTA) on 3 consecutive days. On day 1 baseline values were obtained. On day 2 the subjects were pretreated with 1.5 g MET at 9 a.m., administered orally with milk to avoid severe gastric symptoms. A dose of 1 mg DEX was given orally at 11 p.m. On day 3 administration of 1.5 g MET was performed as described for the day before. Of the subjects 80% experienced a transient dizziness and a hot flush after MET administration, which disappeared spontaneously within 45–60 min.

Assays

Chemicals. [^{3}H]Thymidine (specific activity 25 Ci/mmol) was obtained from Amersham (Buckinghamshire, UK). Phosphate-buffered saline (PBS) was obtained from Boehringer (Mannheim, FRG). Concanavalin A (Con A), phytohemagglutinin A (PHA), PWM and sodium metrizoate-Ficoll were obtained from Sigma (St. Louis, Mo.), and Rotiszint 22 was obtained from Roth (Karlsruhe, FRG). The culture medium consisted of RPMI medium (Boehringer, Mannheim, FRG) containing 2 m*M* L-glutamate (Biochrom, Berlin, FRG) and 0.1 mg/ml gentamicin (Biochrom) with 8% fetal calf serum (Biochrom) added.

Preparation of cells. A mononuclear cell fraction was prepared under sterile conditions by sodium metrizoate-Ficoll density gradient centrifugation (Boyum 1968). Cells were washed two times in PBS for 10 min and incubated for 60 min at 37°C to allow sufficient dissociation of endogenous hormone followed by a third washing procedure. The final concentration of cells was determined using a Coulter Counter (Model S5, Coulter Electronics, UK). Viability of cells exceeded 95%, as judged from their ability to exclude trypan blue. Contamination by erythrocytes was less than 10%; contamination by granulocytes and monocytes was less than 8% and did not differ between the 3 test days and between patients and controls.

Lymphocyte proliferation tests. Lymphocyte proliferation experiments were carried out in plastic microtiter plates in a total volume of 0.22 mL. A quantity of 25,000 cells was incubated in culture medium for 60 h to evaluate Con A- and PHA-generated T-cell mitogenesis and

for 120 h to evaluate PWM-generated B-cell proliferation and glucocorticoid-induced inhibition of spontaneous mitogenesis in a sterile incubator at 37°C in a humidified atmosphere with 5% CO_2. Concentrations of 0.5, 1, 5, 10, 20, 40, and 50 µg/ml were used to evaluate the dose/response curves of Con A- and PWM-induced effects, and concentrations of 0.1, 0.5, 1, 2.5, 5, 10, and 20 µg/ml for determination of the effects of PHA on lymphocyte proliferation. In vitro glucocorticoid effects were assessed by increasing concentrations ranging from 10^{-10} to 10^{-7} *M* DEX on baseline lymphocyte proliferation. A quantity of 0.5 µCi [^{3}H]thymidine was added 5 h prior to termination of the incubation period. Incorporated [^{3}H]thymidine was separated from free nucleotide by rapid filtration through Whatman GF/B filters with a Titertek cell harvester by an 11-s wash with distilled water at room temperature. The filters were transferred into plastic vials, 5 ml of a toluene-based scintillation cocktail was added (Rotiszint 22) and they were monitored for tritium in a Beckman LS 5000 TD counter at about 54% efficiency. All samples were assayed in triplicate with a variation within a single experiment of less than 15%.

Glucocorticoid receptor assay. Binding characteristics of the glucocorticoid receptor (GR) (receptor sites per cell and K_d) were determined using saturation experiments by [^{3}H]dexamethasone as described previously (Rupprecht et al. 1990). One part of the mononuclear cell fraction comprising T- and B-lymphocytes was assayed for GR content immediately after preparation, and the other was used for proliferation experiments in culture.

Hormone assays. The adreno-corticotrophic hormone (ACTH) was measured by an immunoradiometric assay (IRMA) supplied by the Nichols Institute (San Juan Capistrano, Calif.), which does not require extraction procedures (Raff and Findling 1989). A soluble sandwich complex is formed by a ^{125}I-labelled monoclonal antibody directed against N-terminal ACTH and a biotin-coupled polyclonal antibody against C-terminal ACTH. The sandwich complexes are bound by adding avidin-coated plastic beads. Unbound components are washed away and the radioactivity bound to the solid phase is monitored in a gamma counter. The lower detection limit was 1.5 pmol/l, and the intra- and interassay coefficients of variation were 3% and 6.8%, respectively. Values below the detection limit were recorded as 1.5 pmol/l.

Cortisol was measured by a direct radio-immunoassay (RIA) (Stalla et al. 1981). The lower detection limit was 25 nmol/l, and the intra- and interassay coefficients of variation were 5% and 9%, respectively. As there was a cross-reactivity of our cortisol antibody with 11-deoxycortisol of about 15%, determinations of cortisol values following MET administration would not be accurate and were excluded from further analysis.

Data analysis

Lymphocyte proliferation was expressed in terms of a stimulation index defined by the ratio thymidine uptake (DPM) of stimulated/unstimulated leucocytes. The area under the dose/response curves (AUC) (stimulation index * lectin concentrations) was determined using trapezoidal integration.

The results are expressed as the mean ± SD, and as the mean ± SE in the figures. Data were analysed using the *t*-test for paired samples and analysis of variance (ANOVA) for repeated measurements for comparisons within groups, and ANOVA followed by post hoc comparison with Student's *t*-test for comparisons between groups. Correlation data were obtained by Pearson's product-moment correlation. All significance levels are two-tailed.

Results

Administration of MET provoked a marked increase in ACTH in patients and controls, which was avoided by DEX pretreatment (Table 2). ACTH values did not differ between patients and controls following MET administration, indicating an equal amount of 11-β hydroxylase inhibition in both groups. There was a significant increase in GR sites per cells following MET administration in healthy controls, which was not present in depressives (Table 3).

DPM of the unstimulated thymidine uptake of patients and controls are given in Table 4. Depletion of endogenous cortisol by MET and subsequent replacement by DEX did not alter Con A- and PHA-induced mitogenesis in patients and controls (Table 5), and there was no significant difference between the two groups on ei-

Table 2. Mean ± SD adrenocorticotrophic hormone (ACTH) levels (pmol/l) of patients during depression ($n = 12$) and of healthy controls ($n = 13$) under baseline, metyrapone (MET), and MET + dexamethasone (DEX) pretreated conditions, and baseline cortisol values (nmol/l)

ACTH	Patients		Controls	
	Mean	SD	Mean	SD
Baseline	4.2	1.5	3.5	0.8
MET	24.9	19.4	26.4	19.5
MET + DEX	4.0	0.2	1.5	0.1
Cortisol	273.1	104.8	225.7	77.3

Table 3. Mean ± SD glucocorticoid receptor (GR) sites per cell of patients during depression ($n = 12$) and controls ($n = 13$) under baseline, MET and MET + DEX pretreated conditions

	Patients		Controls	
	Mean	SD	Mean	SD
Baseline	3219	1173	3290	787
MET	3110	1114	5495*	2488
MET + DEX	2735	1080	3863	2117

Analysis of variance (ANOVA) for repeated measurements (* $P < 0.01$)

Table 4. Mean ± SD DPM of unstimulated leucocytes (stimulation index = 1) for the dose/response curves for concanavalin A (Con A) and phytohaemagglutinin (PHA) after 60 h culture and for pokeweed mitogen (PWM) and spontaneous lymphocyte proliferation after 120 h culture

	Con A	PHA	PWM
Patients			
Baseline	1012 ± 440	1077 ± 464	2541 ± 1208
MET[a]	908 ± 571	992 ± 528	2753 ± 2465
MET + DEX[b]	932 ± 735	1026 ± 675	2181 ± 2054
Controls			
Baseline	828 ± 528	1023 ± 767	2928 ± 1408
MET	835 ± 396	919 ± 318	3573 ± 2661
MET + DEX	851 ± 373	845 ± 302	2236 ± 2178

[a] Metyrapone
[b] Dexamethasone
The DPM are given for the depressed patients and the normal controls

Table 5. Mean ± SD areas under the stimulation curves for Con A ($AUC_{Con\ A}$) and for PHA (AUC_{PHA}) induced leucocyte proliferation of patients during depression ($n = 12$) and of healthy controls ($n = 13$) under baseline, MET, and MET + DEX pretreated conditions

	Patients		Controls	
	Mean	SD	Mean	SD
Con A				
Baseline	208.2	116.7	267.8	178.1
MET	269.6	203.5	232.2	157.7
MET + DEX	361.0	330.0	272.0	188.6
PHA				
Baseline	413.9	266.3	456.3	266.6
MET	362.2	197.4	348.1	204.8
MET + DEX	381.7	204.2	389.9	214.4

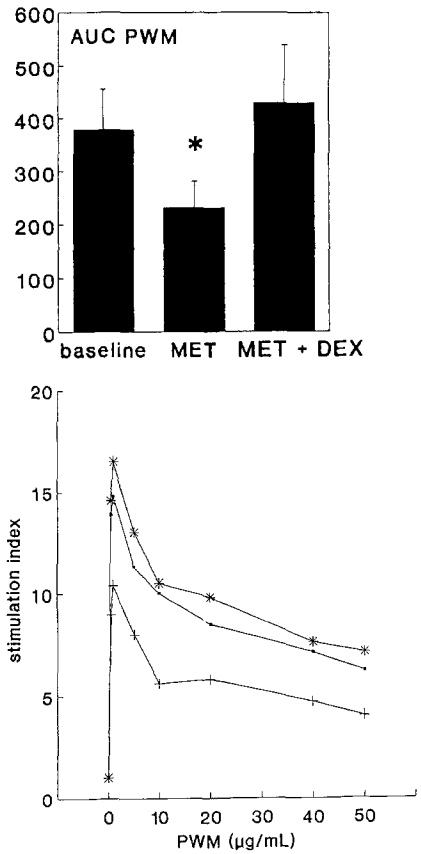

Fig. 1. Mean dose/response curves for pokeweed mitogen (PWM)-generated lymphocyte proliferation at 1600 h on 3 consecutive days under baseline (o), metyrapone *(MET)* (+) and metyrapone plus dexamethasone *(MET + DEX)* (*) pretreated conditions in healthy controls ($n = 13$). SEs are omitted for clarity of presentation. The *inset* shows the mean ± SE areas under the curves (AUC) of the three dose/response curves. The *asterisk* indicates a significant difference between MET pretreated values when compared with baseline or MET + DEX pretreated values

ther test day. While PWM-generated B-cell mitogenesis (AUC_{PWM}) was significantly lower following MET administration when compared to baseline or MET + DEX pretreated conditions in controls (Fig. 1) ($F = 6.3$, $P < 0.03$; $F = 5.3$, $P < 0.05$), a comparable effect was not present in depressives (Fig. 2) ($F = 1.7$, $P < 0.2$; $F = 1.9$, $P < 0.2$).

DEX added in vitro suppressed spontaneous lymphocyte proliferation in a dose-dependent manner in patients and controls (Figs. 3, 4). This effect (AUC_{DEX}) was more marked after 11-β hydroxylase inhibition by MET when compared with baseline or MET + DEX pretreated conditions in controls (Fig. 3) ($F = 6.5$, $P < 0.03$; $F = 12.9$, $P < 0.006$), but not in depressives (Fig. 4) ($F = 0.7$, $P < 0.4$; $F = 3.4$; $P < 0.1$).

There were no significant associations between age, sex, number of depressive episodes, length of the washout period, treatment prior to the washout period, ACTH, cortisol and GR concentrations and any leucocyte proliferation parameters.

Discussion

We could detect neither a significant difference with regard to Con A-, PHA-, or PWM-induced leucocyte proliferation nor in inhibition of spontaneous leucocyte proliferation by in vitro added DEX between depressed patients and normal controls. The higher DPM following PWM stimulation in depressed patients did not reach even trend level. Our results differ from several observations reporting a clear-cut attenuated mitogen response following administration of various lectins in depressed patients (Kronfol et al. 1983; Schleifer et al. 1984; Cosyns et al. 1989). However, the mitogen-induced blastogenesis has recently been attributed more to factors such as age, severity of depression, and hospitalization effects than to the diagnosis itself (Schleifer et al. 1989). It seems likely that the conclusion that there is an impaired lymphocyte function in depression has been premature. We could not dichotomize into subjects with adequate and inadequate DEX suppression test results as done by Lowy et al. (1988), as our subjects were depleted of endogenous cortisol by MET.

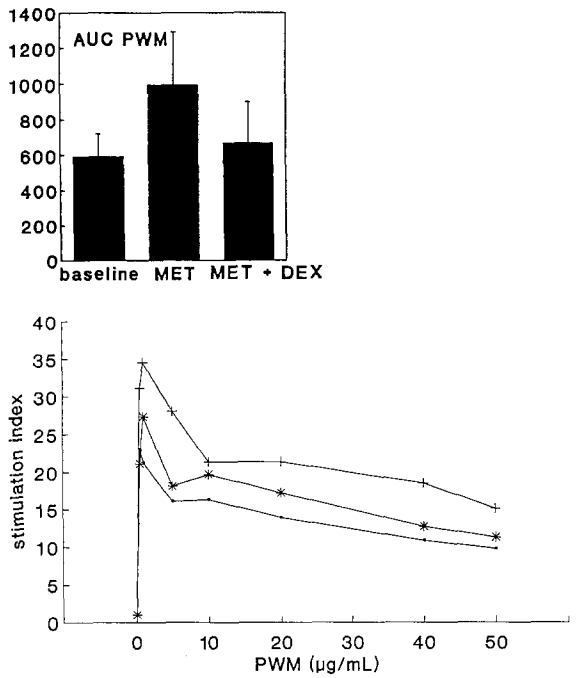

Fig. 2. Mean dose/response curves for PWM-generated lymphocyte proliferation at 1600 h on 3 consecutive days under baseline (o), metyrapone *(MET)* (+) and metyrapone plus dexamethasone *(MET + DEX)* (*) pretreated conditions in depressed patients ($n = 12$). SEs are odmitted for clarity of presentation. The *inset* shows the mean ± SE areas under the curves (AUC) of the three dose/response curves

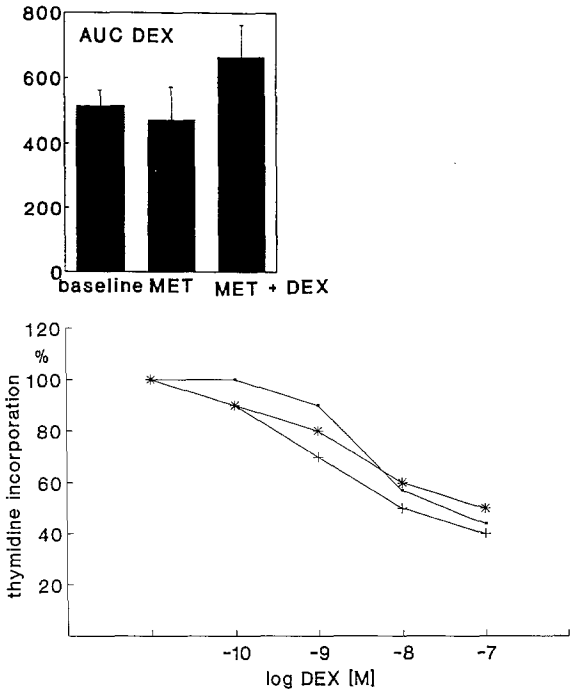

Fig. 4. Mean dose/response curves for dexamethasone *(DEX)* induced inhibition of spontaneous lymphocyte proliferation at 4 p.m. on 3 consecutive days under baseline (o), metyrapone *(MET)* (+) and metyrapone plus dexamethasone *(MET + DEX)* (*) pretreated conditions in depressed patients ($n = 12$). SEs are omitted for clarity of presentation. The *inset* shows the mean ± SE areas under the curves (AUC) of the three dose/response curves

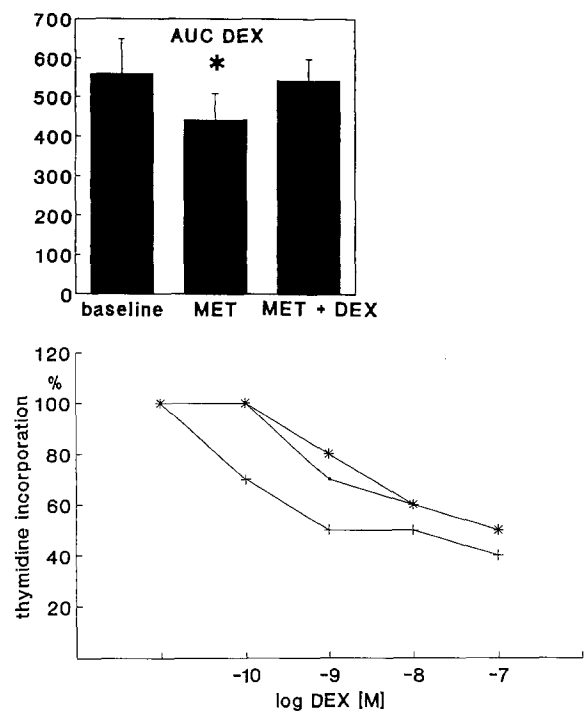

Fig. 3. Mean dose/response curves for dexamethasone *(DEX)*-induced inhibition of spontaneous lymphocyte proliferation at 4 p.m. on 3 consecutive days under baseline (o), metyrapone *(MET)* (+) and metyrapone plus dexamethasone *(MET + DEX)* (*) pretreated conditions in healthy controls ($n = 13$). SEs are omitted for clarity of presentation. The *inset* shows the mean ± SE areas under the curves (AUC) of the three dose/response curves. The *asterik* indicates a significant difference betwen MET pretreated values when compared with baseline or MET + DEX pretreated values

There was a decrease in PWM-induced B-cell proliferation following MET administration in healthy controls which was reversed by DEX administration. As cortisol is an important co-factor for the expression of IL-1 receptors (Akahoshi et al. 1988) and IL-1 plays a major role in the proliferation of B-cells and antibody production, the impaired lymphocyte response to PWM following MET administration might reflect the lack of endogenous glucocorticoids. However, such an effect on MET was not present in the depressed patients. Moreover, depressed patients did not exhibit the enhanced effect of in vitro administered DEX following MET administration as observed in normal controls (Rupprecht et al., submitted). Differences in the rate of 11-β hydroxylase inhibition by MET between patients and controls cannot account for these results, as ACTH and 11-deoxycortisol levels (Rupprecht et al. 1991) are not different between groups following MET administration. Our observations support the hypothesis of a decreased functional plasticity of the glucocorticoid receptor at the cellular level. Previous investigations showed both an attenuated action of glucocorticoid hormones on various endocrine systems in depressed patients (Rupprecht et al. 1987, 1988, 1989) and a diminished autoregulatory potency of the glucocorticoid receptor on leucocytes itself (Rupprecht et al. 1991). In summary, several lines of evidence point to an attenuated action of glucocorticoids at the humoral and cellular level, which might be important for a potential disturbance of the immune-endocrine connection in depression. Since IL-1 immunoreactive

fibres have recently been identified in the paraventricular nucleus of the human hypothalamus (Breder et al. 1988), and IL-1 is capable of increasing ACTH levels and proopiomelanocortin mRNA in the AtT-20 cell (Fukata et al. 1989), it may be concluded that there is a close functional and neuro-anatomical link between the hypothalamic-pituitary-adrenal axis and the immune system which possibly is affected during depressive disorder.

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