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Tricyclic antidepressants inhibit IL-6, IL-1β and TNF-α release in human blood monocytes and IL-2 and interferon-γ in T cells

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Abstract

Tricyclic antidepressants (TCAs) are widely used in treating depressive disorders. It has been demonstrated that, for instance, IL-1β and IL-6 inhibit the HPA axis, which plays a role in the development of depressions. Therefore, we were interested in investigating how TCAs influence cytokine release by T lymphocytes and monocytes respectively. Cells were incubated with either 5 μM clomipramine, 15 μM imipramine or 20 μM citalopram. IL-2 release was suppressed to 60% of the control values by clomipramine and imipramine ($p = 0.001$; $p = 0.000$), but citalopram was found to cause a much weaker inhibition (only 18%) ($p = 0.16$). INF-γ release was affected to a lower degree than IL-2 release, and imipramine (34%) ($p = 0.054$) was more potent than clomipramine (24%) ($p = 0.16$) and citalopram (12%) ($p = 0.059$) in this case. Monocytes incubated with TCA for 4 h exhibited only limited inhibition of IL-1β and IL-6 release, i.e., 6–25% for all three compounds. The corresponding value for TNF-α release was 20–45% inhibition, with citalopram being the weakest inhibitor. After 10 h of monocytes to LPS exposure, all three compounds exerted a strong inhibition of IL-1β and TNF-α release, i.e., 60–70% with p-values below 0.012 for all of them. However the inhibition of IL-6 release was less than 35%. Citalopram was equality as potent as imipramine and clomipramine in inhibiting IL-6 release after long-term exposure of monocytes to LPS. All three TCAs elevated intracellular cAMP concentrations significantly in T lymphocytes and monocytes ($p < 0.001$).

Keywords: Tricyclic antidepressant; Cytokine; Monocyte; T cell; cAMP; In vitro

1. Introduction

Recently, it has been demonstrated that depression is related to activation of cell-mediated immunity (Maes et al., 1995). The evidence for this includes the following: first, a significantly increased CD_4^+/CD_8^+ ratio, which is determined by an increased percentage of T-helper CD_4^+ cells (Darko et al., 1988) and/or by a lowered percentage of T-suppressor cells CD_8^+ (Tondo et al., 1988; Maes et al.,

Abbreviations: ACTH, adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; EDTA, ethylenediamine tetraacetate; ELISA, enzyme-linked immunosorbent assay; FBS, fetal bovine serum; HBSS, Hanks' balanced salt solution; 5-HT, 5-hydroxytryptamine; HPA, hypothalamus-pituitary-adrenal; IFN-γ, interferon-gamma; IL-1β, interleukin-1-beta; IL-2, interleukin-2; IL-6, interleukin-6; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cells; PHA, phytohaemagglutinin; SD, standard deviations; TCAs, tricyclic antidepressants; TNF-α, tumor necrosis factor-alpha

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1992), was observed in patients suffering from major depression. Secondly, T cell activation, as indicated by a significantly increased level of peripheral activated T cells (CD_{25}^{+} and HLA-DR^{+} T cells) and increased serum concentrations of soluble interleukin-2 receptor (Maes et al., 1992; Maes et al., 1993a; Nässberger and Traskman-Bendz, 1993) is seen in such patients. Thirdly, these patients demonstrate an enhanced production of mono- and T-lymphocytic products [e.g., interleukin-1β (IL-1β), interleukin-6 (IL-6) and interferon-γ (IFN-γ) by mitogen-stimulated peripheral blood mononuclear cells (PBMC) (Maes et al., 1991; Maes et al., 1993b; Maes et al., 1994)], as well as high plasma concentrations of IL-1β and IL-6 (Maes et al., 1991) and finally, they also have elevated plasma and urinary neopterin concentrations (Maes et al., 1994; Duch et al., 1984; Dunbar et al., 1992), which is a sensitive marker of activation of cell-mediated immunity (Wachter et al., 1989; Fuchs et al., 1992), together with low serum dipeptidyl peptidase IV activity.

Tricyclic antidepressants are widely used for treating major and minor depression and many such patients undergo chronic treatment. Thus, it is of great interest to investigate whether and, if so, how these drugs affect the human immune system. In our previous studies it has been shown that the antidepressants imipramine, clomipramine, amitriptyline, fluoxetine and citalopram all inhibit transformation of lymphocytes to blastoid forms (Mårtensson and Nässberger, 1993). The results may indicate that antidepressants affect alterations in human immune cells and, therefore, they may also affect cytokine production by immunocompetent cells.

The underlying mechanism by which cytokines are released is still unknown. However, elevation of the intracellular level of cyclic adenosine monophosphate (cAMP) is considered to play an important role in down-regulating the production of cytokines in lectin-induced lymphocytes or LPS-induced monocytes. Certain agents which increase intracellular cAMP concentrations, e.g., prostaglandin E_2, are known to suppress the production of IL-2, IFN-γ (Snijdewint et al., 1993), tumor necrosis factor-α (TNF-α) (Eisenhut et al., 1993) and IL-1β (Viherluoto et al., 1991). The aim of the present study has been to investigate the influence of TCAs on cytokine release by human lympho- and monocytes. Furthermore, we have studied the intracellular concentrations of cAMP in these cells during TCA treatment and in relation to cytokine production.

2. Materials and methods

2.1. Reagents and media

The medium employed was RPMI-1640 with L-glutamine, containing 100 IU penicillin/ml and 100 μg streptomycin/ml (GIBCO, Grand Island, New York) and 10% (v/v) heat-inactivated Fetal Bovine Serum (FBS) (Sigma, St. Louis, MO, USA). Lymphoprep was purchased from Nycomed (Oslo, Norway). Dynabeads M-450 coated with anti-CD19 monoclonal antibodies (Dynabeads M-450 Pan B) were obtained from Dynal (Oslo, Norway). Imipramine and clomipramine were kind gifts from Ciba-Geigy AB (Basel, Switzerland) and citalopram from H. Lundbeck A/S (Copenhagen, Denmark). Ca^{2+}- and Mg^{2+}-free Hanks' Balanced Salt Solution (HBSS), lipopolysaccharide (LPS) from *E. coli* 055:B_5, E-Toxate kit and alpha-naphthyl acetate kit were purchased from Sigma Chemical Co. Phytohaemagglutinin HA16 (PHA-HA16) was obtained from Murex Diagnostics (Dartford, UK).

2.2. Isolation of monocytes and T cells from normal human peripheral blood

Peripheral blood mononuclear cells (PBMC) were isolated from buffy coats by gradient centrifugation on lymphoprep in accordance with the procedure described by Bøyum (1968). Buffy coats from healthy individuals were obtained from the Blood Unit, Sabbatsberg Hospital, Stockholm. PBMC were washed twice in Ca^{2+}- and Mg^{2+}-free HBSS. The monocytes were then incubated for 1 h at 37°C in a humidified CO_2 (5%) incubator to allow the cells to attach to Costar cell culture flasks (non-pyrogenic). After five washes with prewarmed RPMI-1640 medium (37°C), the monocyte-enriched population was then detached by further incubation at 4°C in RPMI-1640 medium containing 10 mM ethylenediamine tetraacetate (EDTA) and 10% FBS for about 20 min. Cells were recovered by gentle pipetting, washed twice and finally resuspended in the culture

medium described above. The purity of monocytes was about 86% as judged by nonspecific esterase staining. Viability as reflected in trypan blue exclusion was always greater than 90%. All medium components and reagents used in these experiments were endotoxin-free, as determined by the Limulus amebocyte lysate assay.

T cells were prepared by depleting the nonadherent fraction (after four rounds of adherence to plastic) of B cells using Dynabeads M-450 Pan B. The cells were resuspended in the culture medium and their viability was greater than 98%, as measured by trypan blue exclusion.

2.3. Experimental design

2.3.1. Cytokine production in mono- and lymphocytes

For determinations of IL-1β, IL-6 and TNF-α release, 10^6 monocytes/well were seeded in 24-well culture plates (non-pyrogenic) (Costar, Cambridge, MA, USA) with 5 μM clomipramine, 15 μM imipramine or 20 μM citalopram (final concentrations). After 24 h preincubation, 10 μg LPS/ml was added and cell-free supernatants were collected after 4 and 10 h-periods of LPS exposure and stored at −20°C until analyzed.

T cells (10^6/well) were cultured in 24-well plates with these drugs at the same concentrations described above. T cells were exposed to 5 μg PHA/ml after 24 h preincubation with the drugs and cell-free supernatants were collected after 24 and 48 h of incubation. The supernatants were stored at −20°C for later analysis of IL-2 and IFN-γ.

The drug concentrations used here were chose on the basis of pilot experiments in which the viability of lympho- and monocytes was tested. The following concentrations were employed 10, 15, 20 and 25 μM imipramine; 5, 8 and 10 μM clomipramine and 20, 30, 40, 60 and 80 μM citalopram.

The highest concentrations which did not affect cell viability (exceeding 90% after 72 h culture) as measured by trypan blue exclusion test were determined and found to be 15 μM for imipramine, 5 μM for clomipramine and 20 μM for citalopram. These concentrations correspond to a 50-, 11- and 50-fold increase compared to therapeutic concentrations. Though even lower concentrations were found to inhibit cytokine release.

2.3.2. Stimulation of cAMP

T cells (0.5×10^6) and monocytes (1.0×10^6) were cultured with 5 μM clomipramine, 15 μM imipramine or 20 μM citalopram (final concentrations). After a 24 h preincubation period, T cells and monocytes were exposed to 5 μg PHA/ml or to 10 μgLPS/ml, respectively, for 15 min and incubations were terminated by adding ice-cold 65% (v/v) ethanol (final concentration) and the wells were washed with ice-cold 65% ethanol. These preparations were centrifuged at 2000 *g* for 15 min at 4°C and the supernatant dried under a stream of nitrogen, and stored at −20°C until assayed.

2.3.3. T cell proliferation assay

In the proliferation studies, 2×10^5 cells were incubated for 3 days under the same conditions as described above. Cultures were pulsed with [^{3}H]thymidine (1 μCi/well) (Amersham, Buckinghamshire, UK) during the last 18 h of this incubation. The cells were then harvested and the radioactivity measured using a scintillation counter (LKB-Wallac 1211 RackBeta Liquid Scintillation Counter). All the cultures were performed in triplicate with controls of untreated lymphocytes in parallel. The percentage inhibition of treated cells was calculated as:[{(cpm of control cultures) − (cpm of cultures containing drugs)} : cpm of control cultures] × 100.

2.3.4. Quantification of cytokines and cAMP

Cytokines were assayed in the cell-free supernatants using the commercially available ELISA kits for human IL-1β, IL-6, TNF-α, IL-2 ("Quantikine™", R&D Systems, Minneapolis, USA) and IFN-γ (Bender MedSystems, Vienna, Austria). The levels of cAMP were quantified using an ELISA technique (Amersham). These assay procedures were performed according to the manufacturer's protocols. Detection limits were 6.0 pg/ml (IL-2); 1.5 pg/ml (IFN-γ); 0.3 pg/ml (IL-1β); 4.4 pg/ml (TNF-α); 0.70 pg/ml (IL-6) and 12 fmol/well (cAMP). The percentage inhibition of treated cells was calculated according to the following formula:

$$\frac{\text{untreated cells} - \text{treated cells}}{\text{untreated cells}} \times 100$$

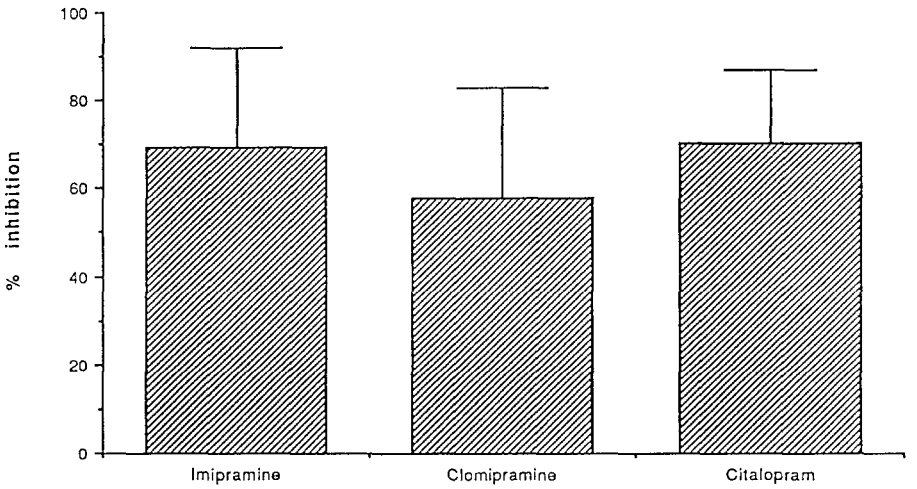

Fig. 1. Effects of the tricyclic antidepressants on [^{3}H]thymidine incorporation by T cells. T cells (2×10^5) from five individuals were preincubated with 15 μM imipramine, 5 μM clomipramine and 20 μM citalopram for 24 h and thereafter stimulated with 5 μg PHA/ml. DNA synthesis in these cells was measured after 3 days in culture, as described in Materials and methods.

2.4. Statistical analysis

The results are expressed as means ± standard deviations (SD). Student's *t*-test were used for statistical analysis of the data.

3. Results

3.1. Influence of antidepressants on T cell proliferation

The effect of antidepressants on PHA-induced ^{3}H-TdR incorporation by T cells from 5 subjects is shown in Fig. 1. When the cells were preincubated with the antidepressants imipramine, clomipramine and citalopram, proliferation of T cells was inhibited by 58–70% compared to non-treated cultures ($p < 0.001$).

3.2. Inhibition of cytokine release by antidepressants

All the three drugs used in our study exerted inhibitory effects on cytokine release by T cells, as well as by monocytes. In general, clomipramine and imipramine were more potent in this respect than citalopram.

Table 1
IL-2 and IFN-γ release by PHA-stimulated T lymphocytes after 24 h preincubation of the antidepressants

		IL-2 (pg/ml) $n = 4$	IFN-γ (pg/ml) $n = 4$
Controls	(24 h)	10329 ± 1040	5532 ± 634
	(48 h)	9002 ± 876	5986 ± 607
Imipramine	(24 h)	4766 ± 1517	3715 ± 1384
	(48 h)	2925 ± 1240	3400 ± 781
Clomipramine	(24 h)	4427 ± 538	4272 ± 1444
	(48 h)	2668 ± 1078	4083 ± 837
Citalopram	(24 h)	8467 ± 2097	5167 ± 1117
	(48 h)	5835 ± 2147	5282 ± 261

T cells (1×10^6) isolated from healthy individuals were preincubated with 5 μM imipramine, 15 μM clomipramine and 20 μM citalopram for 24 hours and thereafter stimulated with PHA (5 μg/ml). The supernatants were collected after 24 and 48 hours of PHA exposure. n = Number of independent experiments.

3.2.1. IL-2 and IFN-γ

T-cells released high levels of IL-2 (10000 pg/ml) and IFN-γ (5500 pg/ml) when exposed to PHA (Table 1). These levels were a 100-fold greater than those seen with unstimulated cells. Imipramine and clomipramine suppressed IL-2 release effeciently (about 60%) after 24 h of exposure ($p = 0.001$; $p = 0.000$), but citalopram was a weaker inhibitor (only 18%) (Fig. 2A). This inhibition was not statistically significant ($p = 0.16$). After 48 h of PHA stimulation, IL-2 release was inhibited an additional 10%, i.e., imipramine and clomipramine caused a 70% inhibition ($p = 0.000$; $p = 0.000$) compared to 30% for citalopram (Fig. 2A) ($p = 0.034$). Inhibition of IFN-γ release was affected to a lower extent than IL-2 release, demonstrating the order imipramine (34%) > clomipramine (24%) > citalopram(12%) (Fig. 2B) ($p = 0.054$; $p = 0.016$; $p = 0.059$). After 48 h of stimulation, the same order of potency was observed and the corresponding inhibitions of IFN-γ release were 43%, 32% and 11% for imipramine, clomipramine and citalopram, respectively. (Fig. 2B).

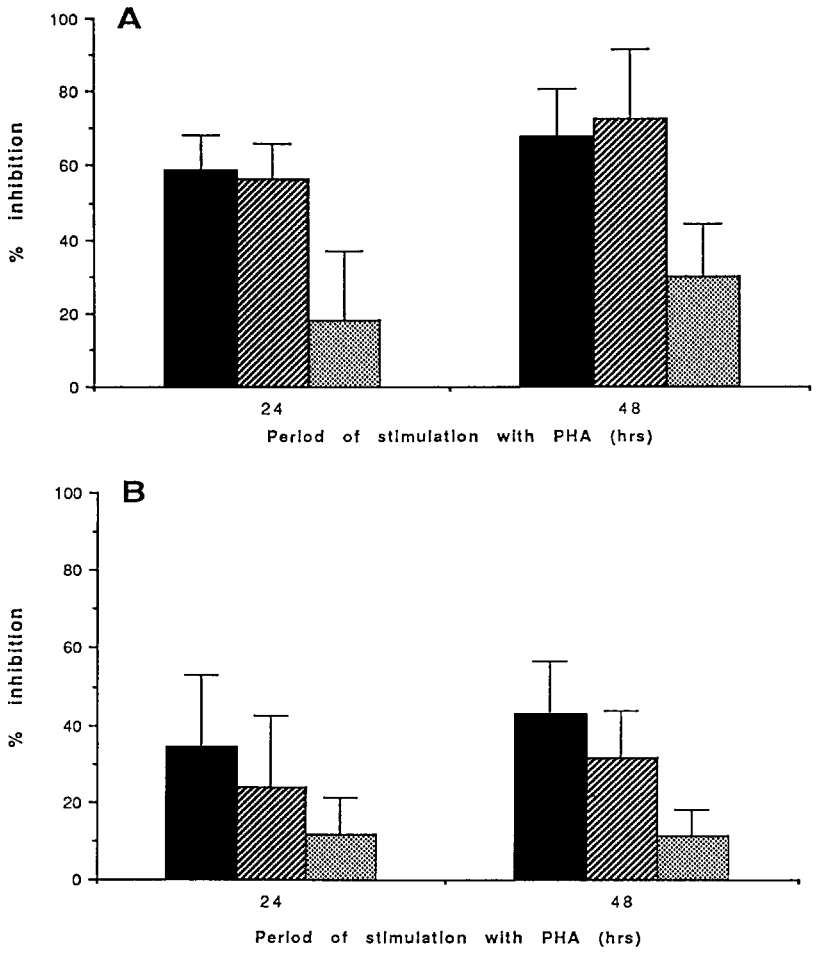

Fig. 2. Inhibitory effects of tricyclic antidepressants –imipramine (dark bars), clomipramine (hatched bars) and citalopram (cross-hatched bars) – on IL-2(A) and IFN-γ (B) release. Inhibition in four independent experiments was calculated as the percentage ± standard deviation of non-treated control cultures.

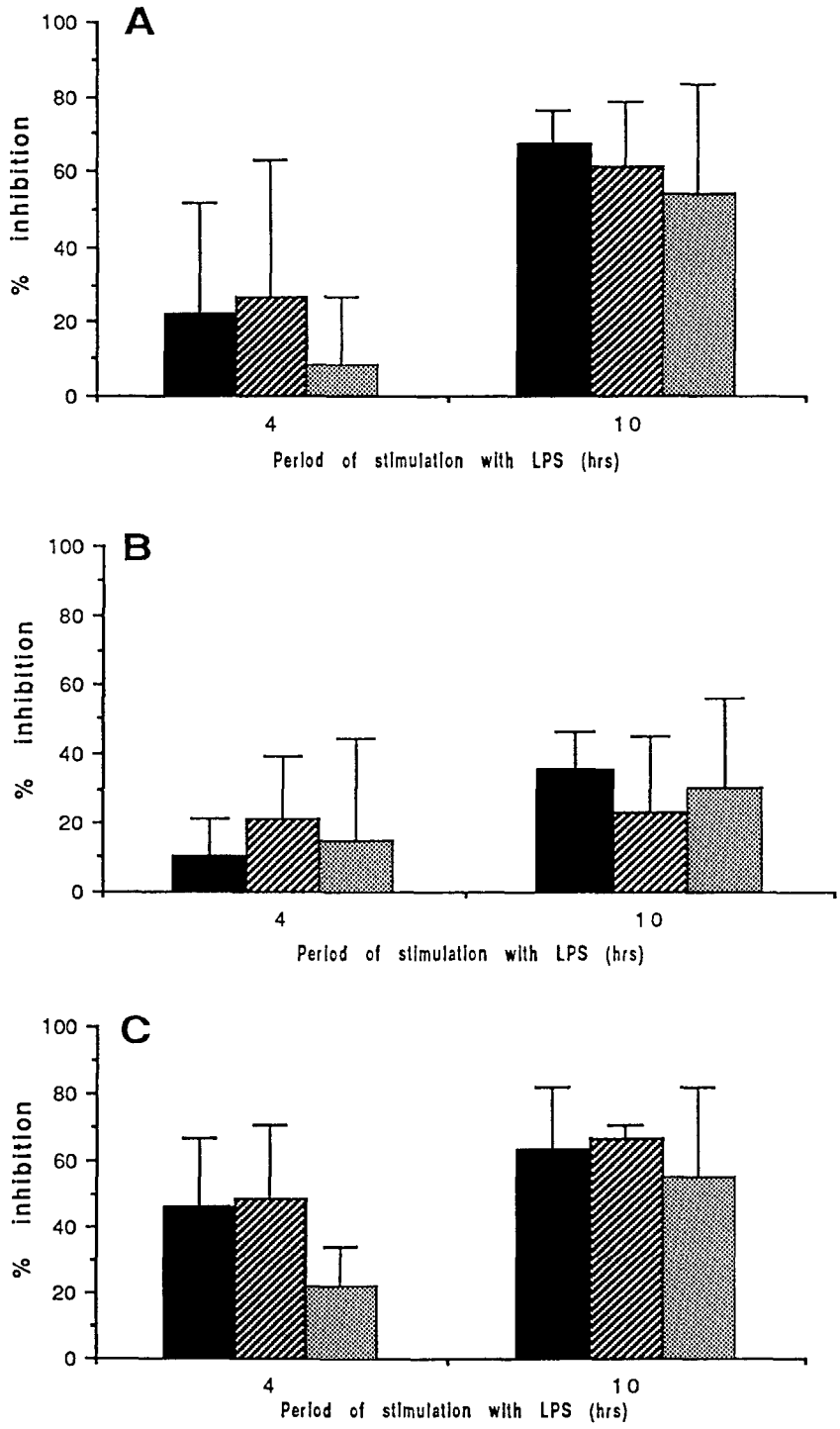
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Table 2
IL-6, IL-1β and TNF-α release by LPS-stimulated monocytes after 24 hours preincubation of the antidepressants

		IL-6 (pg/ml) $n = 4$	IL-1β (pg/ml) $n = 4$	TNF-α (pg/ml) $n = 4$
Controls	(4 h)	2476 ± 259	372 ± 29	5564 ± 482
	(10 h)	1996 ± 163	418 ± 34	722 ± 59
Imipramine	(4 h)	2180 ± 299	294 ± 121	3091 ± 979
	(10 h)	1344 ± 249	135 ± 28	271 ± 149
Clomipramine	(4 h)	1891 ± 707	273 ± 135	2865 ± 1117
	(10 h)	1742 ± 539	155 ± 58	243 ± 43
Citalopram	(4 h)	1893 ± 652	346 ± 99	4266 ± 730
	(10 h)	1391 ± 478	189 ± 123	334 ± 213

Monocytes (1×10^6) isolated from healthy individuals were preincubated with 5 μM imipramine, 15 μM clomipramine and 20 μM citalopram for 24 h and thereafter stimulated with LPS (10 μg/ml). The supernatants were collected after 4 and 10 h of LPS exposure. n = Number of independent experiments.

A statistical significance for imipramine ($p = 0.002$) and clomipramine ($p = 0.01$) but not for citalopram when testing at a 5% significant level ($p = 0.077$).

3.2.2. IL-6, IL-1β and TNF-α

Monocytes incubated with LPS for 4 h showed a high release of IL-6 (2500 pg/ml) and TNF-α (5500 pg/ml), while release of IL-1β was lower around 370 pg/ml (Table 2). After 4 h no significant reduction was seen for any of the 3 TCAs. When the period of LPS stimulation was extended to 10 h, IL-6 release showed a reduction of 19%, and this change showed a borderline statistical significance ($p = 0.054$). However, the corresponding release of TNF-α declined from 5500 pg/ml to 720 pg/ml (an 87% reduction), whereas IL-1β release remained unchanged. The secretory patterns for IL-1β and IL-6, on the one hand, and TNF-α, on the other, were different after 4 h of incubation, with lower release of IL-1β and IL-6. Monocytes preincubated with TCAs exhibited a slight reduction (about 10%) in IL-6 and IL-1β release after 4 h. However, clomipramine suppressed IL-1β release by 27% (Fig. 3A), but the corresponding value for citalopram was only 6%. When monocytes had been stimulated for 10 h, IL-1β release was reduced twice as much as IL-6 release (Fig. 3A + B) with a clear significance for all 3 compounds imipramine ($p = 0.000$), clomipramine ($p = 0.001$) and for citalopram ($p = 0.012$).

Clomipramine and imipramine inhibited TNF-α release between 45–50% (Fig. 3C). Citalopram, on the other hand, was a weaker inhibitor (23%) of TNF-α release compared to these two other compounds during the first 4 h of exposure (Fig. 3C). However, when monocytes were exposed to LPS for 10 h, citalopram was almost as efficient an inhibitor of TNF-α release as imipramine and clomipramine (Fig. 3C).

3.3. Antidepressants increase the intracellular levels of cAMP in T cells and monocytes

The effects of the antidepressants tested on cAMP concentrations in T cells and monocytes are shown in Fig. 4. All three compounds caused an increase in the intracellular levels of cAMP in both T cells and monocytes to 1.33–1.48 times the control value ($p < 0.05$; $p < 0.001$).

4. Discussion

It has been suggested that disturbances in cytokine synthesis can best be studied under dynamic conditions, by stimulating competent cells with poly-

Fig. 3. Inhibitory effects of tricyclic antidepressants – imipramine (dark bars), clomipramine (hatched bars) and citalopram (cross-hatched bars) – on IL-1β (A), IL-6(B) and TNF-α (C) release. Inhibition in four independent experiments was calculated as the percentage ± standard deviation of non-treated control cultures.

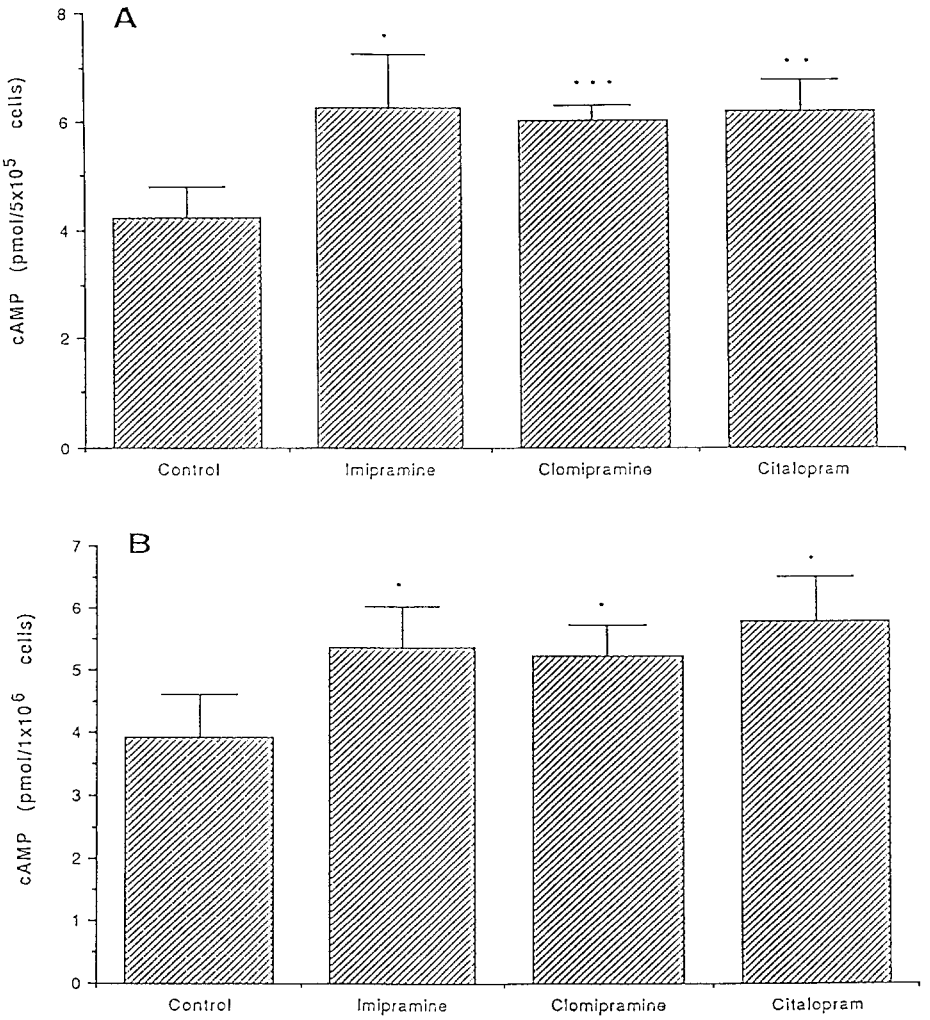

Fig. 4. Effects of the antidepressants on cyclic AMP levels in T cells (A) and monocytes (B). After preincubation for 24 h with 15 μM imipramine, 5 μM clomipramine or 20 μM citalopram, intracellular cAMP levels were measured after 15 min of stimulation with PHA (T cells) or LPS (monocytes). The averages ± SD of values from 4 independent experiments are presented. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to the control values.

clonal activators such as lectins or LPS and thereafter analyzing the pattern of cytokine production (Cavaillon et al., 1990; Ocklind, 1986). Our results show that three tricyclic antidepressants caused an inhibition of IL-2 and IFN-γ release from activated T-cells. Prolonged exposure to the mitogen potentiated this inhibition. A similiar inhibitory pattern was seen for IL-1β, TNF-α and IL-6 release from monocytes and this value was even lower after 10 h exposure to LPS compared to the 4-h incubation period. The order of inhibitory potency was imipramine ≥ clomipramine > citalopram.

Cytokines are a group of signaling molecules involved in communication between cells, including those of the immune system. These substances play an important role in the regulation of many physiological processes and it will certainly be found that these substances interact in as yet unknown, but well-defined manners.

A substantial amount of research concerned with

immunity in relationship to major depression has been carried out during the past decade. Dysfunction of the hypothalamus-pituitary-adrenal axis (HPA-axis) characterized by increased activity, is one of the best documented biological abnormalities associated with major depression (Carroll, 1980). Elevated circulating levels of IL-1β and IL-6 have been observed in depressed patients (Maes et al., 1991). Both IL-1β and IL-6 are pleiotropic, proinflammatory cytokines, which play a central role in the generation of a wide variety of metabolic systemic and behavioral changes. In addition, IL-1β and IL-6 both stimulate corticotrophin-releasing factor, adrenocorticotropic hormone (ACTH) and adrenocortical steroidogenesis.

There is also interaction between interleukins and monoamines. 5-Hydroxytryptamine (5-HT) and norepinephrine, which are involved in the pathophysiology of major depression, have been shown to act as immunoregulators, while cytokines have profound effects on both of these monoamine systems in the brain. For instance, IL-1 augments release of 5-HT, serotonin, noradrenalin, acetylcholine, dopamine and γ-aminobutyric acid, neuro-transmitters that all may be related to the pathophysiology of major depression.

Usually, the antidepressive effect of the tricyclic compounds and their active metabolites is ascribed to their inhibition of the reuptake of 5-HT (serotonin) and/or norepinephrine into monoaminergic neurons. There now seems to be clear evidence for a close relationship between the immune system and psychiatric disorders. It has been reported that IL-1β and IL-6 stimulate the HPA-axis and other neuroendocrine systems which play a role in underlying pathogenetic mechanisms underlying depressive illnesses. Therefore, it may be speculated that TCAs exert part of their antidepressive effect through a down-regulation of the immune system. For instance, as seen in the present study, release of IL-1β and IL-6 is heavily suppressed by all three of the TCAs investigated. To our knowledge, no reports concerning TNF-α and its influence upon neuroendocrine-monoamine functions have been published. However, we found that the TCAs caused a reduction in TNF-α release from monocytes. Whether TNF-α is linked to the HPA-axis, as is the case for IL-1β and IL-6, still remains to be determined.

Furthermore, it has been observed that major depression is associated with a significantly increased number of leukocytes (Kronfol and House, 1989; Irwin et al., 1990). Other effects specific for lymphocytes include an increase in the CD_4^+/CD_8^+ ratio, as well as impaired activity of natural killer cells. Major depression and, in particular, melancholia is accompanied by T-cell activation, as indicated by an increased number of circulating CD_{25}^+ cells (Maes et al., 1992). Morever, increased serum levels of soluble IL-2R are also found in these patients (Nässberger and Traskman-Bendz, 1993).

It is also known that peripheral T lymphocytes and/or their products may act on central regions of the brain (Plata-Salamán, 1991). Furthermore, receptors for cytokines have been found throughout the brain and of particular interest is the observation that these receptors are also present in brain structures linked with depression. Another interesting phenomenon which may be of importance in this connection is penetration, for instance, of IL-1 through the blood-brain barrier, through which activated T cells can also pass. This may indicate that IL-1 and T cells interact with brain cells, binding to specific cell surface molecules and leading to high local concentrations. Therefore, it can be speculated that inhibition of the down-regulation of T cell activity might improve a depressive condition.

In the present study we have demonstrated dramatic effects of TCAs on cytokine release from T cells. In a previous study we have demonstrated that several TCAs are able to block induced lymphocyte transformation in a concentration-dependent manner. The observations made in our present study, with a reduced release of IL-2 and IFN-γ, give further support to the hypothesis that TCAs may exert part of their therapeutic antidepressant efficiency through their effects on the immune system.

The concentrations used in our experimental model are higher than the therapeutic plasma level in patients undergoing treatment but the exposure time do not exceed 72 h. On the other hand in an in vivo situation i.e. in patients, blood cells are exposed to the respective drug for a long period. Therefore the intracellular loading of the drug during in vivo conditions may be equivalent or perhaps even higher despite a lower plasma concentration. However, no doubt that in a clinical situation our findings may be

relevant in particular to adverse consequences of overdose.

The second messenger cyclic AMP plays an important role in T lymphocyte activation, although the exact function of the cAMP pathway in this respect remains unclear. It has been shown that cAMP reverses mitogen- or antigen-induced T cell proliferation, in part by inhibiting of IL-2 production (Mary et al., 1987). We found in our study an increase in intracellular cAMP which corresponds to reduced cytokine synthesis. This is in accordance with other reports (Snijdewint et al., 1993; Eisenhut et al., 1993; Viherluoto et al., 1991).

Chaplin et al. (1980) have demonstrated that stimuli which cause an elevation in intracellular cAMP peak 10–30 min after onset and then gradually decay to baseline values within 2–6 h. Therefore, we chose to measure cAMP levels after 15 minutes of PHA stimulation of cells which had been previously exposed to TCA for 24 hours.

The observed increase in intracellular cAMP may lead to an inhibition of protein synthesis. The prolonged inhibition of cytokine release in this study, up to 48 h, may be due to the fact that cAMP and a cAMP-dependent phosphoprotein inhibits gene transcription and/or post-transcriptional events. This inhibition may last as long as the cells are exposed to TCAs.

In conclusion, the present study demonstrates that the tricyclic antidepressants imipramine, clomipramine and citalopram inhibit cytokine release from human T cells, as well as from monocytes in vitro. This inhibition may be related to the mechanism underlying the therapeutic efficiency of these drugs in patients with major depression, a possibility which should be further explored in the future. However, we would like to point out that this study demonstrates an inhibition of cytokine release only. Although we strongly believe that this reflects reduced synthesis, no experimental support for this hypothesis is presented in the present study.

Acknowledgements

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