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Negative Immunoregulatory Effects of Antidepressants: Inhibition of Interferon-γ and Stimulation of Interleukin-10 Secretion

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There is now some evidence that major depression is accompanied by activation of the inflammatory response system. There is also some evidence that antidepressants may suppress the release of cytokines, such as interleukin-1β (IL-1β) and IL-6 by activated monocytes and IL-2 and interferon-γ (IFNγ) by activated T cells. This study was carried out to examine the effects of clomipramine, sertraline, and trazodone on the stimulated production of IFNγ, a pro-inflammatory cytokine, and IL-10, a negative immunoregulatory cytokine. Whole blood of nine healthy volunteers was stimulated with PHA, 5 μg/mL and LPS, 25 μg/mL for 72 hr with and without incubation with clomipramine, 10^{-6} and 10^{-9} M, sertraline, 10^{-6} and 10^{-8} M, and trazodone, 10^{-6} and 10^{-8} M. All three antidepressants significantly reduced IFNγ secretion, whereas clomipramine and sertraline significantly increased IL-10 secretion in culture supernatant. All three antidepressants significantly reduced the IFNγ/IL-10 ratio. The results suggest that antidepressants, at concentrations in the therapeutical range, have negative immunoregulatory effects through inhibition of IFNγ and stimulation of IL-10 release. **[Neuropsychopharmacology 20:370–379, 1999]** *© 1999 American College of Neuropsychology. Published by Elsevier Science Inc.*

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There is some new evidence that major depression is accompanied by activation of the inflammatory response system (IRS). The evidence includes the following: (1) increased numbers of peripheral blood mononuclear cells (PBMC), such as neutrophils, monocytes, and activated T lymphocytes (Herbert and Cohen 1993; Maes et al. 1992, 1993c; Muller et al. 1993; Sluzewska et al. 1996a, 1996b; Seidel et al. 1996b; Perini et al. 1995); (2) increased secretion of neopterin, a sensitive marker of cell-mediated immunity (Duch et al. 1984; Dunbar et al. 1992; Maes et al. 1994; Bonaccorso et al. 1997); (3) increased secretion of prostaglandin E2 (PGE2) in serum, CSF or culture supernatant obtained after polyclonal stimulation of whole blood (Linnoila et al. 1983; Calabrese et al. 1986; Song et al. submitted; and (4) the presence of a moderate acute phase response, as indicated by increased serum concentrations of positive acute phase reactants, such as haptoglobin, C-reactive protein, and α1-antitrypsin (Maes et al. 1993b, 1995b, 1997a; Joyce et al. 1992; Song et al. 1994; Sluzewska et al. 1996a) and decreased serum concentrations of negative

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acute phase reactants, such as albumin, transferrin, and zinc (Swartz 1990; Maes 1997; McLoughlin and Hodge 1990; Maes et al. 1997b). Activation of the IRS has also been observed in the olfactory bulbectomized and the mild stress rat model of depression (Song and Leonard 1994; Sluzewska et al. 1994).

It is thought that an increased production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-2, IL-6 or interferon-γ (IFNγ) may be orchestrating the activation of the IRS in depression (Maes 1997). There is some evidence for increased (1) production of pro-inflammatory cytokines such as IL-1β, IL-6 and IFNγ in culture supernatant of mitogen-stimulated PBMC; and (2) serum concentrations of IL-6, IL-2, and IL-2 receptor in depression (Nassberger and Traskman-Bendz 1993; Maes et al. 1993a, 1993b, 1994; Sluzewska et al. 1995a, 1995b, 1996a, 1996b; Seidel et al. 1995, 1996a; Frommberger et al. 1997). The above cytokines are known to orchestrate the key steps in the complex network, which regulates responses in cell-mediated and humoral immunity and in the IRS (Cavaillon 1996). Major advances in the understanding of the modulation of cell-mediated immunity and the IRS were the identification of (1) two mutually exclusive populations of T helper (Th) cells (i.e., Th1, which produce IFNγ and IL-2, and Th2, which produce IL-4 and IL-5); and (2) negative immunoregulatory cytokines (i.e., IL-10, which potently suppresses Th1-like effector functions, such as the production of proinflammatory cytokines) (Cavaillon 1996).

It has been suggested that increased production of pro-inflammatory cytokines may play a role in the etiology of depression (Smith 1991; Maes 1997; Yirmiya 1996, 1997). Indeed, IL-1, IL-2, and IFNs given to experimental animals and humans may produce behavioral alterations and symptoms similar to those observed in major depression, such as anhedonia, anorexia, weight loss, social withdrawal, psychomotor retardation, anergy, irritability, sleep disturbances, and malaise (Smith 1991; Yirmiya 1996, 1997; Bluthé et al. 1992; McDonald et al. 1987). If increased production of pro-inflammatory cytokines is at all involved in the etiology of depression one would expect that antidepressive treatments have negative immunoregulatory effects. Recently, Xia et al. (1996) showed clomipramine, imipramine, and citalopram significantly suppressed the secretion of IL-2 by stimulated T lymphocytes and of IL-1β and TNFα by stimulated monocytes. Moreover, there was a trend toward a significant decreased secretion of IFNγ by stimulated T lymphocytes preincubated with the above antidepressants (Xia et al. 1996). Recently, it has been shown that diluted whole blood stimulated with phytohemagglutinin (PHA) + lipopolysaccharide (LPS) offers the most appropriate and reproducible culture condition in order to measure cytokines, such as IFNγ, IL-6, and IL-1 (review: De Groote et al. 1992, 1993; Zangerle et al. 1992). Diluted whole blood cultures reflect the *in vivo* immune cellular and humor interactions and may be employed to examine the effects of any substances or drugs on cytokine secretion (De Groote et al. 1992, 1993). The ratio of IFNγ production/IL-10 production in culture supernatant is of critical importance in determining the capacity of supernatants to activate or inhibit monocytic and T lymphocytic functions (Katsikis et al. 1995).

The aims of the present study were to examine the effects of the tricyclic antidepressant, clomipramine, the selective serotonin reuptake inhibitor (SSRI), sertraline, and the heterocyclic antidepressant, trazodone, on the production of IFNγ and IL-10 (and their ratio) by diluted whole blood stimulated with PHA + LPS.

SUBJECTS AND METHODS

Blood samples for the determination of cytokine secretion were collected from nine healthy volunteers (mean age = 33.1 ± 7.5 years; male/female ratio: 5/4). All subjects gave informed consent after the study design was fully explained. Exclusion criteria for subjects were the following: (1) subjects with a past or present history of psychiatric disorder (axis-1 and axis-2); (2) subjects who ever had been taking major psychotropic medications, such as antidepressants, antipsychotics; (3) subjects with drug (alcohol and any other drug of dependence) abuse; (4) smokers; (5) subjects with any medical (e.g., endocrine, immune, metabolic) disorders, such as diabetes, autoimmune disorders, inflammatory bowel disease, acquired immunodeficiency syndrome; and (6) subjects who currently (2 weeks prior to the first blood sample) suffered from an infectious, allergic, or inflammatory response. The subjects abstained from caffeine and nicotine for at least 8 hr before each session.

After an overnight fast, blood samples for the assays of IFNγ and IL-10 in culture supernatant were taken at 7:30 AM (±30 minutes). Effects of antidepressants on cytokine secretion were studied by stimulating whole blood with PHA and LPS and analyzing IFNγ and IL-10 production in culture supernatant (De Groote et al. 1992). RPMI-1640 medium (Life Technologies, Belgium) with L-glutamine and phenol red and containing 10% of penicillin (Sigma) was employed with (stimulated) or without (unstimulated) 5 μg/mL PHA (Murex, Belgium) + 25 μg/dL lipopolysaccharide (LPS; Sigma, Belgium). 1.8 mL of either one of these two media were placed into 24-well sterile plates, 0.2 mL of whole blood, 1/10 diluted, from each of the nine healthy volunteers was added. The antidepressants were dissolved in sterile water, whereas sterile water alone served as the corresponding control. 20 μL of each antidepressant solution was added to the wells and gently mixed with the medium. Whole blood was seeded in the 24-well culture plates with clomipramine-HCl 10^{-6} and 10^{-9} M, sertraline-HCl 10^{-6} and 10^{-8} M, and trazodone-HCl 10^{-6} and 10^{-8} M. At this low antidepressant-vehicle concentrations and with this small volume of antidepressant solutions, no significant effects on the pH of the buffered whole blood culture may be expected. For each subject, 18 different wells were plated [i.e., 2 (with and without PHA + LPS) × 9 (three with RPMI-medium as control and six with two different concentrations of three different antidepressants)]. Samples were incubated for 72 h in a humidified atmosphere at 37°C, 5% CO2. After incubation, the plates were centrifuged at 1500 rpm for 8 min. Supernatants were taken off carefully under sterile conditions, divided into eppendorf tubes, and frozen immediately at −70°C until thawed for assay of IFNγ and IL-10. The drug concentrations employed here were chosen on the basis of literature on the therapeutic plasma concentrations of these agents. Thus, the 10^{-6} M concentrations employed here are in the therapeutic range of plasma concentrations obtained during clinical treatment, whereas the lower concentrations correspond to subtherapeutical concentrations of the drugs. Nevertheless, the intracellular (e.g., T lymphocytes, monocytes) loading of these drugs in the *in vivo* condition in depressed patients treated with these drugs is difficult to estimate. Clomipramine, sertraline, and trazodone were kind gifts from Ciba-Geigy, Pfizer and Continental Pharma (Belgium), respectively.

IFNγ and IL-10 were quantified by means of ELISA methods (Eurogenetics, Tessenderlo, Belgium) based on appropriate and validated sets of monoclonal antibodies. In short, monoclonal antibodies specific for each component have been pre-coated onto 96-well microtiter plates (Eurogenetics Company, Transporstraat, Tessenderlo, Belgium). Standards and samples were pipetted into the wells and then incubated at 37°C. Cytokines or receptor antagonists were bound by the immobilized antibody and incubated at 37°C. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for each of these components was added to the wells and incubated at 37°C. Following a wash to remove unbound antibody-enzyme reagents, a substrate solution was added to the wells for 10 min. Color development was stopped by sulfuric acid and the intensity of the color was measured by a microtiter plate reader (absorbance at 450 nm). All samples from the normal volunteers were assayed at the same time, in a single run with a single lot number of reagents and consumables employed by a single operator. The intra-assay CV values for both analyses were less than 8%.

STATISTICS

Repeated measure design analyses of variance (RM ANOVAs) were used to examine the (1) within-subject variability with (a) the effect of PHA + LPS treatment as temporal condition and (b) the effects of antidepressant drugs as temporal condition, that is, control (RPMI medium) and the three different drugs; control, 10^{-6} M versus lower concentrations; or control + 6 conditions (two concentrations of the three drugs); and (2) between-subject variability with gender as factor. Repeated measure design analyses of covariance (RM ANCOVAs) were used to examine the within-subject variability with drug treatment as temporal condition, PHA + LPS-induced cytokine secretion as dependent variables and the unstimulated cytokine secretion as covariates. To examine the ratio of the secretion of pro-inflammatory (IFNγ) versus negative immunoregulatory (IL-10) cytokines, the IFNγ/IL-10 ratio was computed as: z transformed IFNγ–z transformed IL-10. Relationships between variables were ascertained by means of Pearson's product moment correlation coefficients.

RESULTS

RM design ANOVAs with stimulation (PHA + LPS stimulated versus unstimulated) and drugs (control versus the six drugs conditions) as within-subject factor and gender as between-subject factor showed significantly higher ($F = 173$, $df = 1/92$, $p < 10^{-4}$) stimulated (mean = 446 ± 277 U/mL) than unstimulated (mean = 43 ± 150 U/mL) IFNγ concentrations and no significant stimulation × drug ($F = .7$, $df = 6/91$, $p = .9$), stimulation × gender ($F = 1.7$, df 1/91, $p = .2$), stimulation × drug × gender ($F = .8$, $df = 6/91$, $p = .5$) interactions, and no significant difference between men and women ($F = .6$, $df = 1/7$, $p = .5$). RM design ANOVAs with the stimulation and drug conditions as within-subject and gender as between-subject factor showed a significantly higher ($F = 704$, $df = 1/91$, $p < 10^{-4}$) stimulated (mean = 651 ± 275 pg/mL) than unstimulated (mean = 63 ± 62 pg/mL) IL-10 secretion and no significant stimulation × drug ($F = 1.1$, $df = 6/91$, $p = .4$), stimulation × gender ($F = 3.4$, $df = 1/6$, $p < .06$) and stimulation × drug × gender ($F = .6$, $df = 6.91$, $p = .7$) interactions, and no significant difference between men and women ($F = .6$, $df = 1/7$, $p = .5$). In the 27 control supernatants (three per subject), we found significant and positive correlations between the unstimulated and stimulated IL-10 ($r = .45$, $p = .01$, $n = 27$), but not IFNγ ($r = -.26$, $p = .1$, $n = 27$), concentrations.

Table 1 shows the effects of antidepressants on the unstimulated IFNγ and IL-10 secretion and on the IFNγ/IL-10 ratio in 18 control supernatants and 3 × 18 supernatants, which were incubated with clomipramine, sertraline, and trazodone (i.e., at the 10^{-6} M and the lower concentrations). Thus, both low and higher concentrations of each of the antidepressants were combined and compared with the negative or positive con-

Table 1. *In Vitro* Effects of Three Different Antidepressant Drugs on the Unstimulated (1) and PHA + LPS-stimulated (2) Secretion of Interferon-γ (IFNγ) and Interleukin-10 (IL-10) in Nine Healthy Volunteers

Variables	Condition	Control	Clomipramine at 10^{-6} M and 10^{-9} M Combined	Sertraline at 10^{-6} M and 10^{-8} M Combined	Trazodone at 10^{-6} M and 10^{-8} M Combined	F[a]	*df*	*p*
IFNγ (U/mL)	(1)	6 (7)	8 (9)	74 (209)	66 (186)	.5	3/60	.7
	(2)	575 (192)	465 (242)[b]	384 (256)[b]	458 (333)[b]	4.8	3/60	.005
IL-10 (pg/mL)	(1)	56 (74)	59 (53)	69 (62)	65 (70)	1.5	3/60	.2
	(2)	547 (251)	665 (230)[b]	680 (253)[b]	658 (348)	2.9	3/60	.03
IFNγ/IL-10 ratio	(1)	−.14 (1.14)	−.17 (0.83)	.16 (1.58)	.15 (1.74)	.7	3/60	.5
	(2)	.72 (0.86)	−.12 (1.03)[b]	−.48 (1.27)[b]	−.12 (1.03)[b]	5.8	3/60	.001

All results are shown as mean (±SD); (1) and (2) denotes the values obtained in unstimulated and stimulated culture supernatants, respectively.
[a]All results of repeated measure design ANOVAs.
[b]All significantly different from the PHA + LPS-stimulated control condition (results of Fisher's LSD at $p = .05$).

trols. RM design ANOVAs with the drug condition as the within-subject factor, showed no significant differences in unstimulated supernatant IFNγ and IL-10 and the IFNγ/IL-10 ratio between the control and antidepressant-incubated supernatants. RM ANOVAs, with the drug condition as within-subject factor, showed that (1) stimulated supernatant IFNγ was significantly lower in supernatants incubated with the three antidepressants than in control supernatant; (2) stimulated supernatant IL-10 was significantly higher in supernatant incubated with clomipramine and sertraline than in control supernatant; and that (3) the stimulated IFNγ/IL-10 ratio was significantly lower in supernatants incubated with clomipramine, sertraline, and trazodone than in control supernatant. RM ANCOVAs with the drug condition as within-subject factor, the stimulated cytokine values as dependent variables, and the unstimulated cytokine values as covariates did not change any of the above results: IFNγ ($F = 4.5$, $df = 3/60$, $p = .007$), IL-10 ($F = 3.0$, $df = 3/60$, $p = .03$), and the IFNγ/IL-10 ratio ($F = 5.8$, $df = 3/60$, $p = .002$).

Table 2 shows the effects of the 10^{-6} M concentration versus the lower concentrations of the three antidepressants on unstimulated and stimulated supernatant IFNγ and IL-10. RM ANOVA with the drug condition as within-subject factor showed: (1) higher unstimulated supernatant IFNγ in supernatants incubated with both concentrations of the antidepressants than in control supernatant; and (2) no significant differences either in unstimulated supernatant IL-10 or the IFNγ/IL-10 ratio between the three conditions. RM ANOVA, with drug condition as within-subject factor, showed (1) significantly lower stimulated IFNγ in supernatant incubated with the 10^{-6} and lower antidepressant concentrations than in control supernatant; (2) significantly higher IL-10 in supernatant incubated with the 10^{-6} concentrations of the antidepressants than in control supernatant; and (3) a significantly lower IFNγ/IL-10 ratio in supernatant incubated with both antidepressant concentrations. RM ANCOVAs with the drug condition as within-subject factor, the stimulated cytokine values as dependent variables, and the unstimulated cytokine

Table 2. *In Vitro* Effects of Antidepressant Drugs (Clomipramine, Sertraline, and Trazodone) at 10^{-6} M and Lower Concentrations on the Unstimulated (1) and PHA + LPS-stimulated (2) Secretion of Interferon-γ (IFNγ) and Interleukin-10 (IL-10) in Nine Healthy Volunteers

Variables	Condition	Control	All 3 Drugs at 10^{-6} M[a]	All 3 Drugs at the Lower Concentrations[b]	F[c]	*df*	*p*
IFNγ (U/mL)	(1)	4 (6)	40 (128)[d]	58 (191)[d]	4.8	2/70	.01
	(2)	575 (199)	390 (264)[e]	481 (287)[e]	10.3	2/70	.0003
IL-10 (pg/mL)	(1)	61 (66)	70 (69)	59 (51)	.4	2/70	.6
	(2)	569 (269)	708 (322)[e]	628 (221)	4.8	2/70	.01
IFNγ/IL-10 ratio	(1)	−.19 (1.06)	−.06 (1.33)	.25 (1.63)	1.7	2/70	.2
	(2)	.59 (0.93)	−.62 (1.03)[e]	.025 (1.11)[e]	13.5	2/70	$<10^{-4}$

All results are shown as mean (±SD); (1) and (2) denotes the values obtained in unstimulated and stimulated culture supernatants, respectively.
[a]Effects of clomipramine 10^{-6} M, sertraline 10^{-6} M, and trazodone 10^{-6} M.
[b]Effects of clomipramine 10^{-9} M, sertraline 10^{-8} M, and trazodone 10^{-8} M.
[c]All results of repeated measure design ANOVAs.
[d]Significantly different from the unstimulated control condition.
[e]Significantly different from the LPS + PHA-stimulated control values (all results of Fisher's LSD at $p = .05$).

values as covariates did not significantly change the above results: IFNγ (F = 7.8, $df = 2/70$, $p = .001$); IL-10 (F = 4.5, $df = 2/70$, $p = .01$); and IFNγ/IL-10 ratio (F = 13.5, $df = 2/70$, $p < 10^{-4}$).

Table 3 shows the effects of the three antidepressants at the two different concentrations on supernatant IFNγ and IL-10 and the IFNγ/IL-10 ratio. RM ANOVA with drug condition (i.e., control and six antidepressant conditions) as the within-subject factor showed no significant differences in the unstimulated IFNγ, IL-10, or the IFNγ/IL-10 ratio between the seven conditions. RM ANOVAs, with drug condition as the within-subject factor, showed a significantly lower stimulated IFNγ/IL-10 ratio in supernatant incubated with clomipramine 10^{-6} M, sertraline 10^{-6} and 10^{-8} M, and trazodone 10^{-6} M in control supernatant. RM ANCOVAs with the stimulated ratio as dependent variable and the unstimulated ratio as covariate did not change these results (F = 3.2, $df = 6/48$, $p = .009$).

DISCUSSION

The main findings of this study are that clomipramine, sertraline, and trazodone have a significant suppressive effect on IFNγ and a significant stimulatory effect on IL-10 secretion by whole blood stimulated with polyclonal activators. These *in vitro* effects were obtained at concentrations in the range of the therapeutic plasma concentrations achieved during clinical treatment with these antidepressants. The finding of the present study suggest that various antidepressive drugs, including SSRIs, tricyclic and heterocyclic antidepressants, may have negative immunoregulatory effects, because they significantly suppress the IFNγ/IL-10 ratio. These results extend those of Xia et al. (1996), who found a trend toward a significant suppression of IFNγ secretion by activated T cells preincubated with tricyclic antidepressants and SSRIs. Our findings that antidepressants have potent negative immunoregulatory effects corroborate the findings of Xia et al. (1996), who found that tricyclics significantly inhibit IL-2 secretion by activated T lymphocytes and that tricyclics as well as SSRIs significantly blunt IL-1β and TNFα release by activated monocytes.

However, while we studied cytokine release by LPS + PHA-stimulated, diluted whole blood, Xia et al. (1996) examined cytokine release by separated T lymphocytes or monocytes. There is evidence that the *in vivo* release of cytokines is better reflected using the LPS + PHA-stimulated, diluted whole blood assay than using "washed" blood assays. Diluted whole blood stimulated with LPS + PHA appears to be an appropriate and reproducible condition of culture to measure cytokine production, whereas isolated PBMC cultivated in media or whole blood stimulated with LPS or PHA

Table 3. *In Vitro* Effects of Three Antidepressant Drugs, (Clomipramine, Sertraline, and Trazodone) at Two Different Concentrations on the Unstimulated (1) and PHA + LPS-stimulated (2) Secretion of Interferon-γ (IFNγ) and Interleukin-10 (IL-10) in Nine Healthy Volunteers

			Clomipramine		Sertraline		Trazodone				
Variables	**Condition**	**Control**	**10^{-6} M**	**10^{-9} M**	**10^{-6} M**	**10^{-8} M**	**10^{-6} M**	**10^{-8} M**	**F[a]**	***df***	***p***
IFNγ (U/mL)	(1)	5 (6)	8 (11)	8 (7)	64 (182)	84 (243)	49 (135)	83 (234)	.2	6/48	.9
	(2)	574 (208)	429 (228)	499 (265)	336 (213)	433 (298)	404 (352)	512 (323)	2.1	6/48	.07
IL-10 (pg/mL)	(1)	56 (73)	59 (57)	60 (52)	75 (72)	62 (53)	75 (84)	55 (55)	.5	6/48	.8
	(2)	548 (257)	717 (261)	614 (196)	659 (270)	702 (249)	750 (437)	566 (218)	1.8	6/48	.1
IFNγ/IL-10 ratio	(1)	−.15 (1.17)	−.16 (0.93)	−.18 (0.83)	−.06 (1.18)	.30 (1.86)	−.15 (1.73)	.40 (1.71)	.6	6/48	.6
	(2)	.81 (0.95)	−.33 (1.06)[b]	.29 (0.90)	−.47 (1.28)[b]	−.27 (1.29)[b]	−.55 (0.76)[b]	.52 (0.98)	3.2	6/48	.009

All results are shown as mean (±SD); (1) and (2) denotes the values obtained in unstimulated and stimulated culture supernatants, respectively.
[a]All results of repeated measure design ANOVAs.
[b]Significantly different from the LPS + PHA-stimulated control values (all results of Fisher's LSD at $p = .05$).

yield a lower reproducibility (De Groote et al. 1992, 1993). Comparing cytokine profiles by diluted whole blood with those of isolated PBMC, it was found that the variability in cytokine production by isolated PBMC is much larger than in diluted whole blood cultures (De Groote et al. 1992). In diluted whole blood, the natural cell-to-cell interactions are preserved. The methods used to isolate PBMC modify the lymphocyte/monocyte ratio, that is, monocyte concentrations may be reduced during the separation process (De Groote et al. 1992). A modified monocyte/lymphocyte ratio in isolated PMBC may influence the outcome of measurements of cytokine production. Because IL-10 is produced by, among others, monocytes, Th0, Th1, and Th2 cells (review: Katsikis et al. 1995) it appears to be important to measure IL-10 in cultures with a preserved monocyte/lymphocyte ratio. In diluted whole blood cultures circulating, endogenous immunoregulatory mediators, either pro-inflammatory or anti-inflammatory, are preserved, whereas isolation of PBMC may eliminate immunomodulatory agents (De Groote et al. 1992, 1993). IFNγ production is higher with LPS + PHA than with LPS or PHA alone (De Groote et al. 1992). This may be explained by synergistic effects of PHA and LPS-induced IL-1 secretion on Th2 cells. Thus, diluted whole blood assays reflect the natural environment, while LPS + PHA stimulation allows the functional characterization of the monocytic and T lymphocytic cytokines (De Groote et al. 1992, 1993). Of course, this standardized method does not allow delineation of the precise contribution from each cell population to the cytokine production. Cultures on isolated or purified monocytes and T lymphocytes, as examined by Xia et al. (1996), may assess the specific mechanisms involved, although this method does not reflect the *in vivo* situation. Nevertheless, the results of the present study and that of Xia et al. (1996) show that antidepressant drugs (i.e., tricyclics, heterocyclics and SSRIs) have negative immunoregulatory effects through suppression of monocytic and T lymphocytic pro-inflammatory cytokines and through stimulation of IL-10 secretion.

Another question is whether these *ex vivo* findings are relevant for the *in vivo* response of the immune-inflammatory system to antidepressants. Phrased differently, consideration of *in vivo* results is needed for a correct interpretation of *ex vivo* data. In this respect, it has been shown that subchronic treatment with fluoxetine, another SSRI, normalized the initially increased serum IL-6 concentrations in depressed patients (Sluzewska et al. 1995a, 1995b). In Wistar rats, an 8-week exposure to mild, unpredictable stress induces a depression-like state with an increased capacity of splenocytes to produce IL-1 and IL-2. The antidepressant effect of repeated administration of imipramine was accompanied by a reduction in IL-1 and IL-2 production (Kubera et al. 1996). A single IP injection of 10 mg/kg desipramine to naive mice increases the capacity of splenocytes to produce IL-10 (Kubera et al. 1998). Subchronic treatment with tricyclic antidepressants and fluoxetine is able to suppress the acute phase response in major depression (Maes et al. 1997a). SSRIs, such as sertraline and fluoxetine, attenuate the acute phase response in the olfactory bulbecomized and chronic mild stress model of depression in the rat (Song and Leonard 1994; Sluzewska et al. 1994). Because an acute phase response in the above conditions is probably driven by hypersecretion of pro-inflammatory cytokines (Maes et al. 1993b), these *in vivo* data are in accordance with the contention that antidepressants have negative immunoregulatory effects *in vitro* and *in vivo*. Not all studies, however, were able to find that short-term treatment with fluoxetine significantly suppressed initially increased serum IL-6 and IL-2R concentrations in major depression (Maes et al. 1995a). Finally, it is generally believed that tricyclic antidepressants have immunosuppressive effects *ex vivo* as well as *in vivo* (review: Miller and Lackner 1989).

As described in the beginning of this article, major depression is associated with an increased secretion of IFNγ (Maes et al. 1994; Seidel et al. 1996a) and increased secretion of neopterin, which production is induced by IFNγ (Maes et al. 1994; Duch et al. 1984; Dunbar et al. 1992; Bonaccorso et al. 1997). In addition, psychological stress in humans significantly increases the stimulated production of pro-inflammatory cytokines, including IFNγ (Maes et al. 1998a). Humans with increased IFNγ and decreased IL-10 secretion and, consequently, all increased IFNγ/IL-10 ratio, show significant stress-induced increments in depression and anxiety (Maes et al. 1998b). Finally, administration of interferons, including IFNγ, results in behavioral effects and mood alterations, including symptoms reminiscent of depression and anxiety (Smith 1991; Gutterman et al. 1982; Weinberg et al. 1988). Because antidepressants decrease the IFNγ/IL-10 ratio, it may be speculated that antidepressants exert some of their antidepressant effects through their negative immunoregulatory capacities.

The exact mechanisms by which antidepressive drugs exert their activity on the stimulated production of cytokines by whole blood is still unknown. These effects might be mediated by nonspecific mechanisms through inhibitory effects on lymphocyte blastogenesis, such as DNA synthesis in lymphocytes or alterations in second messenger cyclic AMP (Xia et al. 1996; Nahas et al. 1979). The existence of receptors on immune cells for serotonergic neurotransmission provides another potential mechanism for the activity of antidepressants on the IRS. There is now some evidence that disorders in the central and peripheral metabolism of serotonin (5-HT) play a role in the pathophysiology of major depression and that antidepressant drugs exert their antidepressive effects through interactions with the serotonergic system (Maes and Meltzer 1995). T lymphocytes constitutively express 5-HT receptors, such as 5-HT1A and 5-HT2A/2C receptors, as well as high affinity 5-HT transporter, whereas macrophages possess a specific active 5-HT uptake system similar in affinity to that of platelets (Aune et al. 1994; Jahnova 1994; Faraj et al. 1994; Jackson et al. 1988). After stimulation with polyclonal activators or IFNγ, monocytes and T lymphocytes release 5-HT (review: Aune et al. 1994). The uptake of [^{3}H]-5-HT by lymphocytes is potently inhibited by antidepressants such as clomipramine, fluoxetine, and fluvoxamine (Faraj et al. 1994). It has been shown that 5-HT has some negative immunoregulatory effects as indicated by the following: 5-HT decreases mitogen-induced T lymphoproliferative responses; 5-HT suppresses lymphocyte DNA synthesis; 5-HT inhibits the migration of mononuclear leukocytes; 5-HT inhibits T-cell activation of normal spleen cells; 5-HT decreases IFNγ-induced major histocompatibility antigen class II expression on macrophages; and 5-HT decreases the synthesis of TNFα by macrophages (Sternberg et al. 1986; Bondesson et al. 1993; Bonnet et al. 1984; Kut et al. 1992). Most importantly, zimelidine, an SSRI, and clomipramine reduce the number of IFNγ secreting cells in mitogen stimulated cell cultures (Bengtsson et al. 1992). The receptors responsible for some of these effects were shown to be the 5-HT1 and 5-HT2A/C receptors (Idova and Cheido 1987; Jahnova 1994; Nordlind et al. 1992). 5-HT1A antagonists and inhibitors of 5-HT synthesis may suppress IL-2-stimulated T cell proliferation and the production of Th1-like cytokines, including IFNγ (Aune et al. 1994). T lymphocytes depleted from their intracellular stores of 5-HT do not longer express the IL-2R after mitogenic stimulation (Young and Matthews 1995). In summary, 5-HT, 5-HT1A, and 5-HT2A/2C receptor antagonists, SSRIs and depletion of intracellular 5-HT are all able to suppress various aspects of the IRS (Smejkal-Jagar and Boranic 1994). Thus, part of the immune effects of SSRI, tricyclic and heterocyclic antidepressants may be explained by their serotonergic activities, such as depletion of intracellular 5-HT stores, increased extracellular 5-HT, and/or 5-HT2A/2C receptor blockade.

There are now other preclinical data showing that antidepressants have a negative immunoregulatory activity and even that effects on cytokine production may play a role in the antidepressant activity of these drugs. First, chronic treatment with antidepressants significantly reduces substance P contents in the striatum, substantia nigra, and amygdala of the rat (Shirayama et al. 1996). Because substance P may induce the production of pro-inflammatory cytokines in human monocytes (Lieb et al. 1996), antidepressants could exert their immunosuppressive action, in part, through effects on substance P. Second, chronic treatment with imipramine induces IL-1 and IL-1R antagonist (IL1RA) mRNA in widespread area of rat brain (Suzuki et al. 1996) and induces a greater effect on IL-1RA mRNA than on IL-1 mRNA. The IL-1RA is a pure antagonist of the IL-1R and, as such, this endogenous molecule may inhibit the biological activities of IL-1 (Dinarello 1994; Dayer and Burger 1994). Third, rolipram a novel antidepressant (Eckmann et al. 1988; Horowski and Sastre-y-Hernandez 1985) does not act on neurotransmitters systems directly, but it potently suppresses the production of pro-inflammatory cytokines, such as TNFα and IFNγ (Sommer et al. 1995; Greten et al. 1995; Angel et al. 1995; Pettipher et al. 1996). Fourth, there is some evidence that TNFα regulates the expression of adrenergic receptors, that TNFα-induced regulation of noradrenaline release is associated with alterations of α2-adrenoceptor (α2-AR) responsiveness and that chronic treatment with desipramine modulates α2-AR functions through an altered expression of TNFα (Ignatowski and Spengler 1994).

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