# The Role of Phospholipase -A2 (PLA2) Enzyme in the Etiology of Depression (*)

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***ÖZET***

*Depresyon bir stresle veya hayvan modellerinde olduğu gibi öğrenilmiş çaresizlikle meydana gelir ve sürer. Stres beyinde norepinefrin (NE) sekresyonunu arttırır, buna ikincil olark beta adrenerjik reseptörlerde down regülasyon olur. Strese ikincil, NE sekresyonunun artışı aynı zamanda NE depresyonuna da yol açar. Aksiyon potansiyeli sinaptik aralığa ulaştığında hücre içine kalsiyum iyonlarının girişinde bir artışı neden olur. Böylece PLA-2'nin aracılık ettiği sinaptik kesecikler presinaptik membranda birleşir ve sinaptik aralığa nörotransmitterler (NE, 5,HT vb.)'in salınımına yol açılır. Bu çalışmada aşırı PLA-2 aktivitesinin 5-HT ve NE depolarını boşaltarak (deplete) predispoze kişilerde (genetik geçişle ?) depresyona yol açabilecği varsayıldı. Bu çalışmada DSM-III-R ölçütleri ve Hamilton Depresyon Ölçeği (HDRS)'e göre depresyon (major depresyon veya distimi) tanısı konulmuş ve daha önce hiç tedavi görmemiş 72 yatan erkek hasta araştırıldı. Kan PLA-2, kortizol, IgA, IgM, östradiol, progesteron, HDL/LDL kolesterol ve 24 saatlik idrarda 5-HIAA düzeyleri tedavi öncesi ve sonrası belirlendi. 6 haftalık tedavi boyunca hastaların depresyon düzeyleri her hafta HDRS ile saptandı. Kullanılan iki antidepreson (imipramine ve fluvoxamine ile HDRS puanlarındaki azalma ve PLA-2 aktivitesindeki düşüş arasında pozitif bir korelasyon bulundu.*

*Anahtar kelimeler: Depresyon, antidepresan ilaçlar, fosfolipaz-A2 enzimi, fluvoxamine, imipramine*

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***SUMMARY***

*Depression continues with, or develops secondary to, a stress or, as in animal models, learned helplessness. Stress increases the secretion of norepinephrine (NE) in the brain and, secondary to this, the down regulation in the ß adrenergic receptors. The increase of NE secretion secondary to stress causes a depletion of NE with time. When the action potential reaches the synaptic cleft, it causes an increase in the entrance of calcium ions into the cell, thus fuses the PLA2 mediated synaptic vesicsles to the presynaptic membrane and causes the secretion of neurotransmitters (NE, 5-HT etc.) into the synaptic cleft. In this study, it was hypothesized that excessive PLA2 activity could deplete 5-HT and NE stores and cause depression in predisposed people (thorough genetic penetrance?). In this study 72 inpatients who were diagnosed as having depression (major depression or dysthymia) according to DSM-III-R criteria and HDRS, and who didn't use medicaments were investigated. Blood PLA2, cortisol, IgA, IgM, estradiole, progesterone, HDL/LDL cholesterol and 5-HIAA levels in 24-hours urine were determined before and after treatment. During the treatment, that continued for 6 weeks, the depression levels of the patients were investigated every week with HDRS.*

*Key words: Depression, andidepressant drugs, phospholipase A2 enzyme, fluvoxamine, imipramine*

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## INTRODUCTION

The amine hypothesis postulates a fuctional deficit in neurotransmitter production or uptake or degeneration of receptor function in the etiology of depression. But it does not explain everything in the etiology of depression [18].

There is a number of replicated biological abnormalities regulated by membrane-bound proteins whose activity can be mediated by phospholipase A2 (PLA2) digestion of their lipid environment. It is possible that more than one system is involved in depression, and PLA2 could influence several systems in the direction of depression.

It may be hypothesized that the occurence of PLA2 activity is increased in depression, leading to a disruption in lipid composition, in turn distrupting the activity of the membrane-bound proteins associated with each of the replicated abnormalities described in depressed patients and pharmacological effects:

**1.** Tyrosine hydroxylase (TH) is rate-limiting step for catecholamine synthesis, and PLA2 regulates its lipid environment and activity (Mandela 84) PLA2 decreases TH [22]. PLA2 degradetes the second messenger phosphatidylcholin while activates TH [1,37].

**2.** Excessive PLA2 activity would inhibit negative feedback, leading to an increased release of CRF and ACTH [18,23]. Many of the depressed patients have an elevated CRF and ACTH and cortisol levels (Table 1).

**3.** The binding of pituitary TRH to the TRH receptor is inhibited by PLA2 hydrolysis of the membrane. Some depressed patients have a blunted response of TSH to TRH [1,11,36].

**4.** Depression is more common in women. Estrogen and progesterone regulate PLA2 in the uterus [3,11, 25].

**5.** Depressed patients have a decreased number of β2-adrenergic receptors. Proper functioning N-regulatory proteins, which are sensitive to changes in membrane structure, are essential for the activation of adenylate cyclase in the β receptor complex [28] Glucocorticoids and tricyclic antidepressants modulate this coupling [18,24,32].

**6.** Depressed patients show [1] increased platelet a2-receptor number (Bmax) [2] no change in a2-receptor binding affinity (Vmax), and [3] receptor subsensivity that is reduced by norepinephrine-induced inhibition of c-AMP production [18]18,41,42].

**7.** As a common feature in depressed patients as well as in the activation of PLA2, Na-K-ATPase activity involved in trans-membrane transport uptake of 5-HT in platelets, imipramine-binding for the labeling of 5-HT receptors is reduced in plateles as well as in brain. Furthermore, the activity of Ca-Mg-ATPase is decreased as well [14,27,31].

**8.** Depressed patients have increased intracytoplasmic calcium levels in the cerebrospinal fluid [10].

**9.** ECT is an effective antidepressant [34]. ECT inhibits PLA2 for prolonged periods via the sustained release of the anticonvulsant prostaglandin-E2. Lithium and ECT are effective in mania as well as in depression. Furthermore steroids can cause depression as well as euphoria. The NE or 5-HT hypotheses have similar problems [18,26].

**10.** S-Adenosyl-methionine (SAMC) is believed to be a rapid and effective antidepressant [6,7]. As SAMC methoylates phosphatidylethanolamine to from phosphatidylcholine, it may be restoring membran components digested by PLA2 and restoring membrane fluidity [18,27]. Furthermore, an anticonvulsant and antimanic agent, valproate, inhibits production of phosphatidylcholine and causes endogenous accumulation of SAMC in rat brain [5,18].

**11.** In contrast to the in vivo application of therapeutic doses, antidepressants (TCAs) such as imipramine, chlorimipramine and desmethylmipramine inhibit PLA2 in vitro. Chlorpromazine was found in double-blind placebo controlled studies to be an antidepressant, inhibiting PLA2 in a variety of tissues and in vitro studies [33,38].

**12.** Alcohol causes changes in membrane lipids [14] and increases PLA2 activity in rats [35] and also re-

**Table 1. The relationship of biological findings in depression to phospholipase-A2 activity (from Hibbeln et al 1989)**

| Human studies in depressed vs normal individuals | | Biochemical studies of $PLA_2$ | |
|---|---|---|---|
| | **CALCIUM** | | |
| Calcium in CSF | ⇑ | Calcium activates $PLA_2$ | ⇑ |
| | **Membrane transport** | | |
| a. Na. K. ATPase activity | ⇓ | $PLA_2$ of FFA on Na-K ATPase | ⇓ |
| b. 5-HTP uptake in plateles | ⇓ | $PLA_2$ activity on 5-HT uptake | ⇓ |
| c. İmipramine binding | ⇓ | $PLA_2$ activity on imipramine binding | ⇓ |
| d. Ca-mg-ATPase activity | ⇓ | $PLA_2$ activity on Ca-Mg-ATPase | ⇓ |
| | **Neurotransmitter receptors** | | |
| **α2 adrenergic receptor** | | | |
| **a.** Receptor number ($B_{max}$) | ⇑ | $PLA_2$ activity receptor number | ⇑ |
| **b.** Bindings affinity ($V_{max}$) | No change | $PLA_2$ activity on binding affinity | No change |
| **c.** NEPI -induced inhibition of cAMP production | ⇓ | $PLA_2$ activity on NEPI-induced inhibited of c-AMP production | ⇓ |
| **β adrenergic receptor** | | | |
| **a.** NEPI and ISOP stimulation of adeniylate cyclase | ⇓ | $PLA_2$ activity on FFA on ISOP stimulation of adenylate cyclase inhibition of N-protein prevents coupling | ⇓ |
| **b.** Effect due to decreased coupling | | | |
| | **Neuroendocrine** | | |
| **a.** Basal cortisol (plasma, urine and CSF) | ⇑ | $PLA_2$ activity inhibits glucocorticoid binding to glucocorticoid receptors; lack of negative feedback causes cortisol to increase | |
| **b.** Cortisol post-dexametasone supression test | ⇑ | | |
| **c.** TSH response to TRH | ⇑ | $PLA_2$ activity inhibits TRH binding to TRH receptor, TSH response is | ⇑ ⇑ |
| | **Neurotransmitters, metabolites, related enzymes** | | |
| **a.** HVA in CSF | ⇓ | Low levels of $PLA_2$ activity can decrease tyrosine hydroxylase activity and would result in decreased HVA and NEPI | ⇓ |
| **b.** 5-HIAA in CSF (suicide) | ⇓ | | |
| | **Other findings** | | |
| **a.** Prostaglandin-E2 in CSF | ⇑ | $PLA_2$ is the rate-limiting step in prostoglanin syntesis | ⇑ |
| **b.** Serum free fatty acids FFA increase with severity of symptoms | ⇑ | $PLA_2$ release FFA in proportion to activity | ⇑ |
| **c.** Phosphatidylcholine decreased in some blood components | ⇓ | $PLA_2$ digests phosphatidlycholine | ⇓ |
| **d.** Alterations in RBC membrane biochemics noted by ESR | | $PLA_2$ perturbs membrane fluidity in smilar manners | |
| **e.** Suicide victims have relatively disposed neuronal membranes | | $PLA_2$ perturbs neuronal membranes | |
| | **Immune function** | | |
| **a.** Response to Con-A stimulation | ⇓ | $PLA_2$ activity on response to Con-A | ⇓ |
| **b.** Lymphocyte number postbreavement | ⇓ | $PLA_2$ activity on lymphocyte mitogenesis | ⇓ |
| **c.** Immune function in depressed patients | ⇓ | $PLA_2$ intimately involved in macrophage function, neutrophil cytotoxicity, and prostaglandin release | ⇓ |

duces membrane control of PLA2 [39]. There is an epidemiological association between alcoholism and depression [18,19,39].

**13.** Depression develops or continues from secondary to a stress like separation from beloved objects or as in animal models, by learned helplessness. Stress increases the secretion of norepinephrine (NE) in brain and, secondary to this, the down regulation in the β adrenergic receptors. The increase of NE secretion secondary to stress causes a depletion of NE with time. When the action potential reaches the synaptic cleft, it causes an increase in the entrance of calcium ions into the cell, thus fusion of the PLA2 mediated synaptic vesicles to the presynaptic membrane and causes the secretion of neurotransmitters into the synaptic cleft. There is substantial evidence that the PLA2 mediates the calcium-induced release of catecholamines in rat brain synaptosomes [19]. Furthermore, β-bungarotoxin, in which PLA2 is the major active component, depletes catecholamine storage in brain synapses. Excessive endogenous PLA2 activity might deplete neurotransmitter stores and cause depression in much the same way by which reserpine depletes neurotransmitter stores and results in depression [18].

**14.** PLA2 releases arachidonic acid, a precursor of series 2 prostaglandins (PGE2-TXA2 etc.). Depressed patients have elevated PGe2 in the CSF and serum and elevated TXA2 in serum [4,19,26]. It is postulated that this elevation caused depression. Aspirin and other nonsteroid antiinflammatory drugs inhibit prostoglandin production, but these affect neither PLA2 nor mood, but cortisol which acts upstream to induced hypomodulin, decreasing PLA2 and consequently prostaglandin release, produces the cortisol euphoria [18].

**15.** The acute phase of depression lowers lymphocyte responte to phytohem aglutinin (PHA) concanavolin-A (Con-A), and pokeweed mitogen (PWM) antigens [40]. Breavement also lower, responses to PHA, Con-A and PWM mitogens in the first 2 months of the postbreavement. Free Fatty Acids (FFAs) released from PLA2 hydrolysis regulates lymphocyte response to Con-A, cell surface hydrolysis regulate lymphocyte response to Con-A, cell surface capping and lymphocyte mitogenesis [18].

Fluvoxamine is a selective 5-HT reuptake inhibitör [8]. Efficacy data are availale from open trials and controlled comparison with both placebo and TCA's, fluvoxamine significantly superior to placebo [8,12,21]. Most of studies indicated that fluvoxamine is at least as effective as imipramine, and also flovoxamine has less intolerable side effects than imipramine [2,8,9,12,16,30].

In this study it was postulated that a dysfunction of PLA2 is an inherited predisposing factor and when coupled with stress leads to an increased fusion of NE or 5-HT vesicles to membrane and depletion of amines, as well as changes in critical membrane-bound proteins, enzyes and receptors. This hypothesis is highly speculative and is clearly an unproven possibilty. Our aim was to provide a contribution to this hypothesis.

## MATERIAL and METHODS

The research group was constituted by 72 inpatients of the Psychiatry Clinic of the School of Medicine, Gülhane Military Medical Academy of Haydarpaşa Training Hospital, who had the diagnosis of dysthymia and major depression according to DSM-III-R criteria. Physically and mentally healthy 20 males constituted the control group. Demographic features of the patient and control group are shown in Table 2. The criteria for being included and excluded in this study are listed in Table 3 and 4. Blood specimens without anticoagulant were allowed to coagulate for 1/2 hour. After centrifugation for 10 min. (300 rpm) the serum was stored in -40°C.

Serum phospholipase A2 activity was measured using phospholipase-A2 kit obtained from Boehringer-Mainheim. This is a colorimetric method using the wavelength 546 nm (Hg) for the measurements.

1 U/L is the enzyme activity releasing 1 µmol/L fatty acid in 1 minute.
Normal values: 0-10 U/L IM serum (37° C).

Parametric and nonparametric tests were used for statistical evaluation of the data (student's t test, Mann Whitney-U-test, Wilcoxon matched pairs, and spearman correlations, all two tailed).

**Table 2. Demographic features of patients and control gruops**

| | Fluvoxamine group (n=42) | İmipramine group (n=30) | Controls (n=20) |
|---|---|---|---|
| Age (mean year) | 21.3±1.1 | 21.2±1.3 | 22.6±1.2 |
| Mean duration of illness/year | 1.3±1.2 | 1.2±1.2 | -- |

**Table 3. Criteria for inclusion in the study**

1. To fit in DSM-III-R, major depression and dysthymia criteria
2. Acceptance of hospitalization
3. 17 items hamilton depression rating scale being minimum 15 p.
4. 18-60 age group

**Table 4. Criteria for exclusion from the study**

1. Narrow-angle glaucoma
2. Prostate hypertrophy
3. Severe, uncontrolled diabetes
4. Serious liver, kidney, heart and respiratory system disease
5. Severe asthma and other allergic conditions
6. Cancer
7. Alcoholism
8. The use of MAOI's at least two weeks ago
9. The use of liver enzyme inducers (e.g. barbiturates)
10. Therapy with other antidepressants
11. Drug dependence
12. The use of ECT at least a month on a more recent time
13. Lithium therapy

Patients with the diagnosis of major depression and dysthmia according to the criteria of DSM-III-R and having at least 15 points from the 17-items HDRS were randomely divided into two groups. The patients were set upon fluvoxamine and imipramine 100 mg/day respectively. After one week, the doses were increased to 150 mg/day and applied for 5 weeks.

## RESULTS

PLA2-levels of the research and control groups before and following treatment are shown in Table 5 no significant differences were detected here.

In the group of the patients with major depression, pretreatment blood cortisol levels were, on average, found to be significantly elevated ($p<0.01$) compared with the respective values of the control group and of the patients with major depression after treatment. Hormone (progesterone, estrogene) levels as well as values of IgM, IgA, HDL, LDL cholesterol were found to be not significantly altered when compared within the research groups themselves and with the control group.

5-HIAA levels before treatment and in 24 hours urine were found to be slightly decreased in the research group, but there was no significant difference compared with the values of the control group.

The responsiveness to the antidepressant therapy was evaluated according to HDRS on the days 0,7,14 and 42 (Table 7).

The positive correlation was found between the two antidepressants used, the lowering HDRS scores and decrease of PLA2 levels.

## DISCUSSION

The results of this study show fluvoxamine is at least as effective as imipramine in the treatment of depression. These findings are in accordance with the literature [9]. There are many previous controlled studies of fluvoxamine and imipramine in literature. Four showed trends toward superiority of fluoxamine to imipramine on HDRS scores [1,2,12,21]. Three demonstrated opposite trend [16,17,20]. The study by Norton et al: 1984 is difficult to classify since active drug effects were weak in the entire sample.

The side effects expressed as subjective complaints were somewhat more frequent in the imipramine group, though only "drymouth" was found to be statistically significant ($p<0.05$), other than these, complaints like insomnia, headache, agitation, nausea were reported more in the two drug groups in re-

**Table 5. Comparison of the PLA2 levels research and control gruops**

| | Flovoxamine group (n=42) | | Imipramine group (n=30) | | Control group (n=20) |
|---|---|---|---|---|---|
| | Major depression | Dysthymia | Major depression | Dysthymia | |
| Before treatment | 4.419 | 4.190 | 4.386 | 4.112 | 3.987 |
| Following treatment | 3.918 | 3.910 | 3.814 | 3.821 | |
| Before treatment | 2.752 | 2.020 | 3.127 | 2.478 | 2.123 |
| Following treatment | 2.482 | 2.418 | 2.986 | 3.114 | |

* *p >0.05*

**Table 6. Comparison of blood cortisol levels of research and control group**

| | | Flovoxamine group (n=42) | | Imipramine group (n=30) | | Control group (n=20) |
|---|---|---|---|---|---|---|
| | | Major depression (n=22) | Dysthymia (n=20) | Major depression (n=20) | Dysthymia (n=10) | |
| Mean (mg/dl) | Pretreatment | 23.808* | 20.166* | 21.112* | 20.178* | 9.188 |
| | Posttreatment | 16.477* | 14.978* | 16.676* | 15.140* | |
| SD | Pretreatment | 3.253 | 3.976 | 3.447 | 3.580 | 3.926 |
| | Posttreatment | 5.162 | 6.114 | 6.714 | 6.646 | |

* *p<0.01*

**Table 7. The HDRS scores of the patients for D-0, D-7, D-14, and D-42 (n=72)**

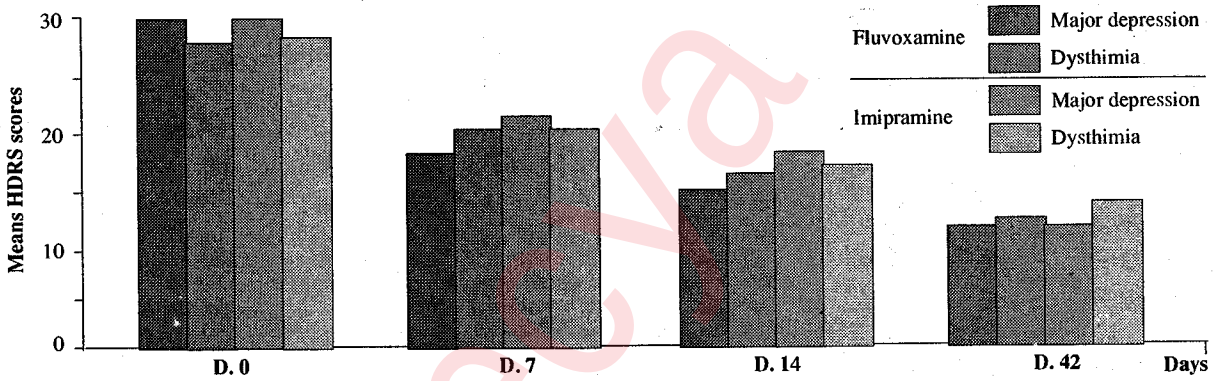
| Drug | Illness | Days of treatment | | | | Statistical significance comparison of two drug groups |
|---|---|---|---|---|---|---|
| | | D - 0 | D - 7 | D - 14 | D - 42 | |
| Fluvoxamine group (n=42) | Major depression group (n=22) | 29.6* (±12.8) | 18.4* (±8.6) | 15.1* (±4.2) | 10.4* (±4.3) | Non - significant |
| | Dysthimia group (n=20) | 26.8* (±6.4) | 20.2* (±4.8) | 15.8* (±4.6) | 10.7* (±4.4) | Non - significant |
| Imipramine group (n=30) | Major depression group (n=20) | 29.4* (±13.1) | 20.4* (±8.2) | 18.8* (±5.1) | 10.5* (±4.6) | Non - significant |
| | Dysthimia group (n=10) | 27.1 (±6.6) | 20.1* (±6.1) | 16.5* (±4.6) | 11.2* (±4.8) | Non - significant |
| Healthy controls (n=20) | | 6.02 (±6.4)* | | | | |

* *(p<0.01) significant compared with D-0*

**Table 8. Comparison of prior to treatment PLA2 activity of patient groups and healthy controls**

| | | Mean (X) (U/liter) | Standart deviation (SD) | Significantly |
|---|---|---|---|---|
| Major depression group (n=42) | Before treatment | 4.396 | 2.988 | NS |
| | Following treatment | 3.879 | 2.396 | |
| Dysthimia group (n=30) | Before treatment | 4.138 | 2.198 | NS |
| | Following treatment | 3.897 | 2.184 | |
| Healthy controls (n=20) | | 3.987 | 2.123 | NS |

*NS: not significant, *: p<0.05 (Prior treatment of $PLA_2$ of major depressive group versus, after treatment of M. depressive group and healthy controls).*




*(p<0.01) Significant compared with day-0 (D-0).*

**Figure 1.** Time course of the diagram of HDRS mean scores at D-0, D-7, D-14, and D-42

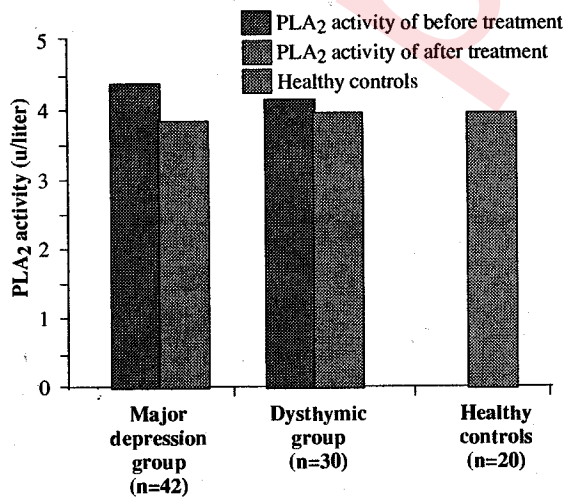



**Figure 2.** Comparison of prior to treatment $PLA_2$ activity of patient groups and healthy controls.

lation to these complaints was not found to be statistically significant. On the other hand, complaints like fatigue, dizziness, tremor, constipation, sweating, was found to be more frequent in the imipramine group at all. But still those complaints in the imipramine group were not statistically significant. All these results are in accordance with literature (8,12,15,16,17,30).

Since our hospital is a military hospital, a great percentage of the patients are 20-22 age group males. Although this may seem to be a disadvantage at first sight, we believe that since it procudes homogenity (which is a very important method necessity in any drug study), it turns out to be an advantage.

This research supports the efficacy and safety of fluvoxamine in the treatment of inpatients with depression. Fluvoxamine treated patients improved significantly more than those who received imipramine. There were fewer complaints of adverse effects and fewer drop outs, premature terminations due to side-effects among the fluvoxamine patients.

Comparison of the PLA2 activities prior and following treatment in the fluvoxamine and imipramine group showed no statistical difference. In patients with schizophrenia and the those with disorders other than schizophrenia (in depression, atypical depression etc.) as well as in the healthy control individuals. The PLA2 activity was increased, but not statistically significant. In depression blood cortisol levels are in general elevated [13,19].

Comparison of blood cortisol levels of patient groups and healthy controls showed that the levels were significantly ($p<0.01$), higher in patient groups than in controls. These findings are in accordance with the literature [1,11,18].

The positive correlations was found between the two antidepressants used, HDRS scores decrease of PLA2 activity.

In this study we made an attempt to evaluate the hypothetic role of PLA2 in the etiology of depression, using patients with major depression and dysthymia. We are of the opinion that PLA2 activity could be of importance in the etiology of depression. For affirming this, extensive and multicentric studies, however, would be of uttermost importance.

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