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# BIOCHEMICAL EFFECT OF ANTIDEPRESSANT DRUGS ON BRAIN AND LIVER ENZYMES IN RABBITS

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## Abstract

*This work aimed to study is the effect of certain antidepressant drugs such as Amitriptyline (Tricyclic antidepressant), Maprotiline (Heterocyclic antidepressant), and fluoxetine (serotonergic agent) on some brain and liver enzyme activities .Sixty male New-Zealand rabbits , were randomly divided into 4 groups each of 15 rabbits as follow:Group I: (Control rabbits) Group II: received Amitriptyline (3.5 mg/kg body weight)orally and daily for 4 weeks., Group III: administered with Maprotiline orally daily (2.33 mg/kg body weight) for 4 weeks. Group IV: administered the therapeutic dose of Fluoxetine (0.93 mg/kg body weight) orally and daily for a duration of 4 weeks.The obtained data revealed that, the anti-depressant drugs caused a marked decrease in brain and liver Monoamine oxidase (MAO) activities,and a very highly significant increase in brain and liver Cholinesterase ( ChE) activity a long the periods of experiment. Regarding Brain and liver alkaline phosphatase (ALP) activity, the btained results demonstrated a highly significant increase in its activity, whereas The obtained results revealed that brain and liver 5' nucleotidase (5'NT) activity showed a highly significant decrease along the experiment. Also The obtained results revealed that Amitriptyline and Maprotiline caused highly significant increase in brain creatine kinase (CK)activity a long the experimental periods. On the other hand, Fluoxetine resulted in significant decrease in brain and liver CK activities*

## Introduction

Depression in the elderly is a predominant health care problem, due to the progressive aging of the population. It results from psychosocial stress, polypathology, as

well as some biochemical changes which occur in the aged brain and can lead to cognitive impairments, increased symptoms from medical illness, higher utilization of health care services and increased rates of suicide and nonsuicide mortality (Carert et al., 2000). Therefore it is very important to make an early diagnosis and a suitable pharmacological treatment, not only for resolving the acute episode, but also for preventing relapse and enhancing the quality of life.

Depressive disorders were resulted from activity of one neurotransmitter, possible interactions between the noradrenergic system and a selective serotonin uptake inhibitor (Bourdeaux et al., 1999). So the efficacy of antidepressant drugs in major depression, panic disorder, obsessive-compulsive disorder, peptic ulcer disease, enuresis, chronic pain migraine, bulimia, and attention deficit disorder is briefly recorded (Goodman and Charney, 1985). Moreover studies concerning the mechanism of action of antidepressants have been performed using the biochemical indicators of the activity of cholinergic neurons as the tricyclic antidepressant. Their mechanism of action is usually attributed to their ability to inhibit catecholamine reuptake into adrenergic nerve endings (Shiber et al., 1998). The Maprotiline (Ludiomil, Novartis) is a tetracyclic antidepressant, which appears to act by blocking noradrenalin uptake at brain synapses where Fluoxetine, a selective inhibitor of serotonin uptake, is clinically useful in treating depression and may be useful for management of variety of other psychiatric and metabolic derangements (Egashira et al., 1999).

The antidepressive therapy induced severe acute hepatitis and after their withdrawal, the patient s fatigue symptoms, sclerotic jaundice, and marked increase of liver enzyme completely disappeared (Braun et al., 1998).

The elevations in serum CPK or LDH enzymes as potential biochemical markers of tricyclic antidepressant (TCA) cardio toxicity may occur in-patients after TCA overdose and the selective serotonin reuptake inhibitor medications (sertraline) caused elevation

of creatine kinase activity in patient treated with massive sertaline overdose (Brendel et al. 2000 ).

Accordingly, this study is to elucidate the effect of administration of certain antidepressant drugs such as Amitriptyline (Tricyclic antidepressant), Maprotiline (Heterocyclic antidepressant), and fluoxetine (serotonergic agent) on some brain and liver enzymes activities as monoamine oxidase (MAO), cholinesterase (ChE), 5-Nucleotidase (5'NT), Alkaline phosphatase (ALP) and creatine Kinase (CK) in rabbits. Which may help to clarify the side effect and metabolic changes which may occur as a result of the antidepressant drugs administration.

## Materials and Methods

### Experimental animals :

Sixty white male New-Zealand rabbits of 2-months old and weighing 1.5 kg were used in these experiments. Rabbits were housed in separate metal cages; fresh drinking water was supplied from automatic fountains, and kept at constant environmental and nutritional condition throughout the experiment. The rabbits were left 14 days for acclimatization before the start of the experiment.

The animals were fed on constant ration from Atmedia Company for production of poultry ration A.R.E. throughout the course of the experiment in the form of pellet rabbit diet then they were randomly divided into 4 groups each of 15 rabbits as follow:

**Group I :** (Control rabbits) comprised 15 animals, received no drug, used as control group and administered with physiological saline.

**Group II:** Consisted of 15 rabbits received Amitriptyline (3.5 mg/kg body weight) orally and daily for 4 weeks.

**Group III:** Included 15 rabbits administered with Maprotiline orally daily (2.33 mg/kg body weight) for 4 weeks.

**Group IV:** Comprised 15 rabbits administered the therapeutic dose of Fluoxetine (0.93 mg/kg body weight) orally and daily for a duration of 4 weeks.

**Sampling :**

One third of the rabbits were scarified after one, two and four weeks of drugs administration. Brain and liver tissue specimens were taken and immediately removed of both (control and experimental groups) washed several times with saline and blotted between two damp filter papers, weighed and then processed directly for determination of: Monoamine oxidase (MAO) [EC 1.4.3.4.] (McEween, 1969). Cholinesterase (ChE) [EC 3.1.1.7] (Den Blawen et al., 1983) Alkaline phosphatase (ALP) [EC 3.1.3.1] (Bertrand and Buret, 1982), and Creatine Kinase (CK)[EC 2.7.3.2.] (Rosano et al., 1976).

## Results and Discussion

The obtained data revealed that, administration of antidepressant drugs caused a marked decrease in brain and liver MAO activities along the experimental periods. These results are similar to those observed by Celada and Artigas (1993) who recorded that five tricyclic antidepressants, Amitriptyline, clomipramine, desipramine, imipramine and prindole have comparable potencies as inhibitors of monoamine oxidase in rodent brain and liver (Tables 1 and 2).

These changes could be attributed to a direct effect of thyroid hormone as confirmed by Campos-Barros et al. (1995) who suggested that MAO inhibitory modulator concentration in rat heart cytosol was increased by the administration of thyroxin to rats and thyroid hormone regulates membrane-associated MAO activity via the production of MAO inhibitory modulators, that the modulators probably bind to specific sites on the outer mitochondrial membrane, and that this binding of modulators to the membrane may result in a structural change in the mitochondrial membrane and a decrease in MAO enzyme activity (Obata and Yamanaka, 2000).

The obtained data showed a very highly significant increase in brain and liver ChE activity along the periods of experiment. The results agreed with those of (Bekpinar et al., 1994) who showed that, long term of administration of Psychotropic drug and tricyclic

antidepressive drug in rats resulted in a significant increase in brain cortex acetylcholinesterases. Furthermore, Barcellos et al. (1998) investigated that the increased enzymatic activity in rabbits treated with antidepressants may be due to accelerated turnover of acetylcholine, possibly through the blockade of dopaminergic receptors, that increased acetylcholine turnover might cause adaptive changes in enzymes for acetylcholine synthesis and degradation (Mahadik et al., 19880) and may be partly due to they effect a variety of membrane properties such as membrane expansion and membrane fluidization and additionally conformational changes of membrane proteins are the main consequences of drug-membrane interaction. Thus, it is conceivable to suggest that alterations lead to an increase in membrane-bound cholinesterase activity (Bekpinar et al., 1994).

Regarding Brain and liver ALP activity, the obtained results demonstrated a highly significant increase in its activity. These findings were in agreement with (Abdel Raheem et al., 1996 and 1997) who observed that administration of antidepressant drugs. Amitriptyline hydrochloride (tryptizol) and imipramine hydrochloride (tofranil) in rats induced a highly significant increase of 21.78% and 4.58% in hepatic and brain ALP activity, respectively. The increase in enzyme activity may be attributed to disturbances particularly; those in the cell membrane permeability and concurrent sever a granulocytosis and elevation of transaminases (Alderman et al., 1993).

The obtained results revealed that brain and liver 5-NT activity showed a highly significant decrease along the experiment which could be attributed to the changes of cellular permeability due to the release of glucocorticoids and its effect on the activity of enzymes located in cell membranous reactions. As confirmed by (Moriwaki et al., 1999) who reported that the decrease of 5-NT could be explained because adenosine may modulate thyroid hormone secretion and the hypothyroid state induced by methylthiouracil caused a decrease of the activity of 5-NT

in (liver, kidney, lung and brain) tissue of rats. Moreover, the hypothetical mechanism of the effect of thyroid hormones on the processes of feed back regulation of oxidative phosphorylation and delivery of substrates and oxygen is presented.

The obtained results revealed that Amitriptyline and Maprotiline caused highly significant increase in brain creatine kinase (CK)activity a long the experimental periods. On the other hand, Fluoxetine resulted in significant decrease in brain and liver CK activities

Regarding to liver CK showed highly significant decrease in Fluoxetine group, these results agree with Brendel et al. (2000) who concluded that, elevations in serum CPK or LDH enzymes as potential biochemical markers of tricyclic antidepressant cardio toxicity may occur in patients after overdose. These decreases in brain and liver CK activities in Fluoxetine and Amitriptyline could be attributed to the depressed protein content in liver and brain that may be due to inhibition of protein synthesis and/or enhancement of protein catabolism (Abdel Raheem et al., 1996) due to retarded in corporation of amino acids into proteins. It appears that, the drugs drastically affect the tissue protein synthesis machinery.

So it is recommended that the clinical use of antidepressant drugs specially the tricyclic one should be used in ordinary doses and avoid the large doses. Moreover, it should be under supervision of specialized physician in psychiatric diseases.

**Table (1):** Effect of Amitriptyline, Maprotiline and Fluoxetine administration on brain enzymes (Mean±S.E.).

| | MAO (µ/g tissue) | | | ChE (µ/g tissue) | | | ALP (µ/g tissue) | | | 5-NT (µ/g tissue) | | | CK (µ/g tissue) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks |
| ***Control (group I) (x±S.E.)*** | 33.21 ±0.90 | 35.22 ±1.22 | 31.29 ±0.86 | 591.0 ±5.4 | 632.5 ±3.8 | 642.0 ±3.00 | 2.30 ±0.09 | 1.96 ±0.05 | 1.85 ±0.13 | 4.83 ±0.13 | 4.88 ±0.18 | 4.04 ±0.18 | 418.0 ±5.6 | 416.8 ±5.8 | 432.8 ±5.3 |
| ***Amitriptyline (group II) (x±S.E.)*** | 18.07 ±1.06** | 29.28 ±0.85* | 30.60 ±0.81 | 638.0 ±5.3** | 726.0 ±5.6** | 698.0 ±7.4*** | 2.85 ±0.13* | 2.38 ±0.10* | 2.10 ±0.16 | 4.06 ±0.11* | 4.90 ±0.14 | 2.80 ±0.13** | 490.0 ±8.42** | 437.8 ±3.20* | 433.8 ±3.32 |
| ***Maprotiline (group III) (x±S.E.)*** | 27.01 ±0.86* | 28.64 ±1.20* | 27.04 ±0.49* | 995.0 ±5.2** | 968.0 ±4.5*** | 1010.0 ±6.5*** | 3.46 ±0.22* | 2.76 ±0.40** | 4.80 ±0.19** | 4.08 ±0.25* | 3.85 ±0.06** | 2.23 ±0.06** | 455.3 ±3.7** | 455.8 ±3.3** | 498.0 ±3.0** |
| ***Fluoxetine (group IV) (x±S.E.)*** | 32.44 ±1.11 | 30.01 ±1.33* | 23.81 ±1.48** | 797.0 ±5.2*** | 836.0 ±6.5*** | 877.0 ±5.3*** | 3.86 ±0.74* | 3.33 ±0.22** | 4.24 ±0.26** | 3.60 ±0.14** | 2.70 ±0.12** | 2.34 ±0.11** | 398.0 ±3.2* | 372.0 ±4.14** | 388.3 ±4.13** |

**S.E.: Standard Error.**
***: Significant at (P<0.05)** ****: highly significant at (P<0.01)** *****: Very highly significant at (P<0.001)**

**Table (2): Effect of Amitriptyline, Maprotiline and Fluoxetine administration on liver enzymes (Mean±S.E.).**

| | MAO (µ/g tissue) | | | ChE (µ/g tissue) | | | ALP (µ/g tissue) | | | 5-NT (µ/g tissue) | | | CK (µ/g tissue) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks | One week | Two weeks | Four weeks |
| *Control (group I) (x±S.E.)* | 47.03 ±0.83 | 48.12 ±0.84 | 50.72 ±0.95 | 943.5 ±7.3 | 985.0 ±4.5 | 945.0 ±5.7 | 68.00 ±1.08 | 69.75 ±1.04 | 56.75 ±0.82 | 8.72 ±0.33 | 7.40 ±0.31 | 7.72 ±0.3 | 276.0 ±5.2 | 369.0 ±4.8 | 366.0 ±6.2 |
| *Amitriptyline (group II) (x±S.E.)* | 35.71 ±1.76*** | 38.62 ±2.10* | 48.55 ±1.18 | 1415.5 ±4.3*** | 1318.8 ±4.8*** | 1322.5 ±4.5*** | 69.36 ±1.21 | 98.70 ±3.60** | 63.05 ±1.55* | 6.72 ±0.32* | 3.70 ±0.23** | 4.10 ±0.10** | 260.5 ±7.6 | 317.7 ±4.2** | 335.0 ±5.0* |
| *Maprotiline (group III) (x±S.E.)* | 35.04 ±1.74** | 45.21 ±2.65 | 48.57 ±1.68 | 1244.0 ±2.5*** | 1181.8 ±4.8*** | 1333.0 ±2.8*** | 68.10 ±2.43 | 77.15 ±3.10 | 79.70 ±2.24** | 7.36 ±0.17* | 4.70 ±0.18** | 7.70 ±0.15 | 256.0 ±3.3 | 337.0 ±4.1 | 346.0 ±5.3 |
| *Fluoxetine (group IV) (x±S.E.)* | 34.17 ±2.08** | 40.98 ±2.70* | 31.10 ±0.95** | 1134.8 ±3.0*** | 1016.0 ±3.8*** | 1054.5 ±5.9*** | 54.40 ±2.50* | 55.40 ±2.34* | 52.20 ±1.04 | 3.40 ±0.11** | 8.50 ±0.26 | 7.60 ±0.19 | 270.0 ±5.0 | 322.0 ±3.2* | 326.0 ±4.0* |

S.E.: Standard Error.

*: Significant at (P<0.05) **: highly significant at (P<0.01) ***: Very highly significant at (P<0.001)

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