

REVERSAL OF STRESS-INDUCED MEMORY CHANGES BY MOCLOBEMIDE: THE ROLE OF NEUROTRANSMITTERS

*Elżbieta Nowakowska[#], Alfons Chodera, Krzysztof Kus,
Przemysław Nowak*, Ryszard Szkilnik**

Department of Pharmacology, Karol Marcinkowski University of Medical Sciences, Fredry 10, PL 61-701 Poznań, Poland, *Department of Pharmacology, Silesian Medical University, H. Jordana 38, PL 41-808 Zabrze, Poland

Reversal of stress-induced memory changes by moclobemide: the role of neurotransmitters. E. NOWAKOWSKA, A. CHODERA, K. KUS, P. NOWAK, R. SZKILNIK. Pol. J. Pharmacol., 2001, 53, 227–233.

Studies on animals have shown that chronic stress is able to evoke behavioral changes such as locomotor activity deficit, decreased sleep, reduced food and water consumption and impaired memory. Chronic stress produces changes in concentrations of neurotransmitters, mainly in the hippocampus. The hippocampus is a vulnerable brain structure that is involved in learning and memory functions.

In this study, we investigated the effects of chronic stress procedure and moclobemide in rats, and the influence of chronic stress on the levels of monoamines: noradrenaline (NE), dopamine (DA) and serotonin (5-HT) in the rat hippocampus [as well as their metabolites: dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA)]. It was found out that chronic 21-day stress caused worsening of memory: the well trained rats after stress procedure lost their ability to find food quickly. Because of many errors in finding the way, the time these animals needed was on average 2.4-times longer than that of the control group. Single, as well as prolonged (21 days) treatment with moclobemide (10 mg/kg/day) counteracted the deficit of memory induced by chronic stress. In stressed animals, we observed an increase in DA, decrease in DOPAC, 5-HT and 5-HIAA and decrease in NE levels. Moclobemide modulated the changes in the levels of neurotransmitters in the hippocampus, decreasing their turnover.

The results demonstrate that moclobemide improves memory impaired by stress. They suggest also that moclobemide has a modulatory effect on stress-induced neurotransmitter changes which may be of importance for the protective effect of the drug with regard to memory impairment.

Key words: stress, moclobemide, memory, hippocampus, monoamines, corticosterone, rats

[#] correspondence

INTRODUCTION

Studies on animals have shown that chronic stress results in sleep disturbances, decreased appetite and decreased water consumption, and impairs memory [15, 16, 26]. These behavioral disturbances bear similarities to clinical depression with respect to etiology, symptomatology and responsiveness to antidepressant treatment and are often used as animal models of depression [3, 41].

The hippocampus is a sensitive brain structure that is involved in certain aspects of learning and memory [9]. This part of the brain may also play some role in the etiology of depression. Its dysfunction occurs both in schizophrenia and in affective disorders [26]. Stress is another factor damaging the hippocampal structures. Repeated immobilization procedures produce atrophy of dendrites of CA₃ pyramidal neurons in rats [21, 29, 39]. The stress reaction is characterized both by behavioral and neuroendocrinological disturbances, controlled by the hypothalamo-pituitary-adrenal axis (HPA). This HPA axis and pathological adaptation to stress are the factors responsible for the stress-induced depression.

The acute stress increases the release of the corticotropine releasing factor by the hypothalamus neurons and, thus, stimulates the release of the adrenocorticotrophic hormone (ACTH) and corticosteroids [7, 21, 26].

It has also been revealed that intensified stress causes the release of stress-dependent endogenous neurohormones, such as epinephrine and norepinephrine, which have a significant influence on cognitive functions: vigilance, motivation, learning and memory [14, 17, 38].

Moclobemide is known as an antidepressant and a reversible inhibitor of type A monoamine oxidase [10], which may improve cognitive functions. Many authors postulate also its anxiolytic activity in animals and in humans [18, 33].

In this study, we investigated the effects of chronic stress procedure on memory in rats and the influence of moclobemide on memory in chronically stressed rats. For the purpose of elucidation of the role of monoamines and the HPA axis during stress, we also investigated the influence of chronic stress on the levels of NE, DA, 5-HT concentration (as well as their metabolites) in the hippocampus of rats, and the interference of moclobemide. We determined the plasma levels of corticosterone after

chronic stress and moclobemide administration in rats.

MATERIALS and METHODS

Animals

Male Wistar rats, 180–200 g, bought from a breeder (licence of the Ministry of Agriculture in Warszawa, Poland) were used in this study. The animals were housed in standard laboratory conditions under a 12 h light/dark cycle, light on at 6 a.m., in a temperature controlled room at $21 \pm 2^\circ\text{C}$, humidity 60%, with free access to granulated standard food and tap water. The rats were kept four per cage (30 × 30 × 20 cm).

Drugs

Sodium carboxymethyl cellulose pure (CMC) (Koch-Light Laboratories Ltd., London, England); moclobemide (p-chloro-N-(2-morphinoethyl)-benzamide), RO 11-1163 (Hoffmann-La Roche, Basel, Switzerland); corticosterone (Sigma, Germany); (³H) corticosterone – 77 Ci/mmol (Radioactive Centre Amersham); an antiserum against corticosterone was obtained from Biogenesis.

Moclobemide (10 mg/kg) was suspended in 0.5% solution of CMC and administered *per os* (*po*) 30 min before the test. In the chronic experiments moclobemide was administered to rats for 3 weeks.

Methods

The experimental part of our research was done on animals with all respect to ethical issues concerning experimenting on animals (UNESCO, 15.10.1978, Paris).

Memory assessment

Memory was evaluated in the labyrinth food finding test (maze test). Before the test, the animals were deprived of food (rats were individually housed with limited access to food – 3 pellets per day) but had unlimited access to water. The rats were trained in the maze test during 2 weeks, with food placed in the end-point of a complex route. The food was the reward for finding the way. The animals were put always in the same place of the maze (start place), only one animal at a time. Every two days the rats were fed without limitations (after the test) for 30 min. After a two-week training,

only those rats were selected for the test which needed less than 30 s for finding the way to food. The mean time in the 4 groups before starting the experiment (without drugs) was similar – between 22–25 s. During the tests CMC (control group) and moclobemide were administered.

Chronic stress procedure

Chronic stress procedure was a variant of the method described by McKittrick et al. [29]. For 21 days the rats were immobilized once a day for 2 h in a plastic frame with a flexible wire mesh sheet. Each rat was held tightly in place by this wire mesh sheet. Each test was performed 24 h after the last session of chronic stress.

Determination of corticosterone by radioimmunoassay method

Concentration of corticosterone was determined by radioimmunoassay method of Przegaliński et al. [35], after protein precipitation as described by Abraham [1].

Determination of NE, DA, DOPAC, 5-HT, 5HIAA

Rats were killed by decapitation and the hippocampus was dissected. The tissue was dissolved by sonication in ice-cold 0.1 M perchloric acid containing 0.05 mM ascorbic acid, and the samples were centrifuged at $15000 \times g$ for 20 min at 4°C.

The NE, DA, DOPAC, 5-HT and 5HIAA levels in the samples were measured according to Magnusson et al. [22] by high-performance liquid chromatography with electrochemical detection (Gilson, France).

The composition of the mobile phase was: 75 mM $\text{Na}_2\text{PO}_4 \times 2\text{H}_2\text{O}$, 1.7 mM 1-octanosulfonic acid, 5 mM EDTA, 100 mM triethylamine, and phosphoric acid (pH 3). The flow rate was 0.5 ml/min, and the potential was +700 mV. Peaks were automatically integrated by the data module and quantified with external standards. The used instrumentation included: a Hypersil BDS C 18 column (ThermoQuest GB), a pump 302 (Gilson, France), an electrochemical detector (Gilson, France) and a data module 802 C.

Statistics

The statistical significance of the results of the memory trials was performed by the Mann-Whitney U-test to compare each of the treatment

with respective control. All the data are expressed as means \pm SEM.

Statistical data for biochemical analysis were analyzed by two-way analysis of variance followed by ANOVA test for grouped data and by Dunnett's test for comparison with the control.

RESULTS

Stress and moclobemide effects on memory

Chronic stress caused a worsening of memory, and the well trained rats after repeated stress lost their ability to quickly find food. Because of many errors in finding the way, the time they needed was on average 2.4 times longer than the time of the control rats (Tab. 1 and 2).

Table 1. The effect of moclobemide given at a single dose in stressed and unstressed rats on the food finding time in the maze

Drug	Dose (po)	Food finding time [s] [$\bar{x} \pm \text{SEM}$]
Control group	0.5 ml of 0.5% CMC	26.8 \pm 1.3
Chronic stress group	0.5 ml of 0.5% CMC	52.8 \pm 1.6*
Moclobemide	10 mg/kg	17.0 \pm 1.4*
Chronic stress + moclobemide	0.5 ml of 0.5% CMC + 10 mg/kg	32.6 \pm 4.2 ⁺

Each test was performed on 8 rats after 1 day of stress and 30 min after moclobemide or CMC administration. * Statistically significant differences ($p < 0.05$) vs. control group. ⁺ Statistically significant differences ($p < 0.05$) vs. the group subjected to chronic stress and moclobemide-treated group (Mann-Whitney test)

Moclobemide administered at a single dose of 30 min before the test, caused a significant improvement of memory (Tab. 1). After chronic treatment, this effect could not be shown (Tab. 2). Moclobemide used as a single dose and in chronic treatment (21 days) prevents worsening of memory caused by chronic stress (Tab. 1 and 2).

The influence of stress and moclobemide on plasma corticosterone levels in rats

Chronic stress caused increased plasma concentration of corticosterone in rats (99.0 ng/ml in control group and 202.0 ng/ml in the group subjected to chronic stress). Prolonged treatment with mo-

Table 2. The effect of moclobemide after prolonged treatment in stressed and unstressed rats on the food finding time in the maze

Drug	Dose (po)	Food finding time [s] [$\bar{x} \pm \text{SEM}$]
Control group	0.5 ml of 0.5% CMC	17.9 \pm 1.5
Chronic stress group	0.5 ml of 0.5% CMC	49.3 \pm 4.2*
Moclobemide 21 days	10 mg/kg	17.2 \pm 1.5
Chronic stress + moclobemide 21 days	0.5 ml of 0.5% CMC + 10 mg/kg	34.2 \pm 2.1+*

Each test was performed on 8 rats after 1 day of stress and 21 days after moclobemide or CMC administration. * Statistically significant differences ($p < 0.05$) vs. control group. + Statistically significant differences ($p < 0.05$) vs. the group subjected to chronic stress (Mann-Whitney test)

clobemide at the dose of 10 mg/kg once daily during 21 days produced slight increase in concentration of corticosterone (119 mg/kg) as compared with the control group and counteracted increase in corticosterone level caused by chronic stress (Tab. 3).

The influence of stress and moclobemide on the levels of NE, DA, 5-HT and their metabolites in rat hippocampus

Chronic stress significantly increased the levels of DA, 5-HT and DOPAC in the rat hippocampus, but did not change NE and 5-HIAA levels (Tab. 4) Prolonged treatment with moclobemide (10 mg/kg po once daily during 21 days) increased the levels of DA, NE and 5-HT, but did not change the level of DOPAC and decreased the level of 5-HIAA both in the group treated with moclobemide and in the moclobemide-treated group subjected to stress.

The latter results can be summarized as follows: although moclobemide raises the levels of DA, NE and 5-HT, it decreases 5-HIAA levels or, at least, prevents the increase in DOPAC level.

DISCUSSION

The findings reported here show that the chronic stress procedure weakens working memory functions in rats. This observation is in agreement with

Table 3. The influence of stress and moclobemide on plasma corticosterone level in rats

Drug	Dose (po)	Concentration of corticosterone in plasma [ng/ml \pm SEM]
Control group	0.5 ml of 0.5% CMC	99.0 \pm 2.4
Chronic stress group	0.5 ml of 0.5% CMC	202.0 \pm 2.8*
Moclobemide (21 days)	10 mg/kg	119.0 \pm 2.8*
Chronic stress + moclobemide (21 days)	0.5 ml of 0.5% CMC + 10 mg/kg	156.0 \pm 1.9+*

Each test was performed on 8 rats. * Statistically significant differences ($p < 0.05$) vs. control group. + Statistically significant differences ($p < 0.05$) vs. stressed group (two-way analysis of variance followed by ANOVA test and Dunnett's test)

Table 4. The influence of stress and moclobemide administration for 21 days on the levels of NE, DA, 5-HT and their metabolites in the rat hippocampus

Drug po	Hippocampus levels (ng/g of fresh tissue) [$\bar{x} \pm \text{SEM}$]				
	DA	DOPAC	5-HT	5-HIAA	NE
Control group CMC	7.8 \pm 1.2	69.8 \pm 4.5	193.6 \pm 9.9	288.4 \pm 12.9	450.7 \pm 13.1
Chronic stress CMC	15.2 \pm 1.3*	137.4 \pm 18.6*	242.8 \pm 12.4*	280.6 \pm 14.7	430.7 \pm 14.2
Moclobemide 10 mg/kg	34.8 \pm 12.3*	59.2 \pm 7.8	353.0 \pm 37.9*	209.9 \pm 19.4*	556.5 \pm 33.6*
Chronic stress + moclobemide	28.2 \pm 4.0 ⁺	69.2 \pm 7.8 ⁺	431.3 \pm 16.3 ⁺	227.5 \pm 12.4 ⁺	684.8 \pm 31.9 ⁺

Each test was performed on 8 rats. * Statistically significant differences ($p < 0.05$) vs. control group. + Statistically significant differences ($p < 0.05$) vs. the group subjected to chronic stress (two-way analysis of variance followed by ANOVA test and Dunnett's test)

the results of the studies by Luine et al. [19] who observed that repeated stress applied for 21 days impaired initial learning in a radial maze task [19].

The same results were observed by McEwen et al. [26] who reported that repeated restraint stress applied for 3 weeks caused changes in the hippocampal formation, as well as impairment of initial

learning of the radial arm maze task in rats. Moclobemide, the selective inhibitor of MAO-A, reversed stress-induced memory deficit both after single and multiple administrations.

In our earlier studies we found out that moclobemide improved memory and reversed memory deficit induced by earlier administration of scopolamine [33]. These results are in accordance with the results obtained by other authors [40]. As our earlier studies [34] confirmed the memory improving effect of the drugs that increase 5-HT concentration at receptor site [34], it is quite possible that memory improving effects of moclobemide may be related to the inhibition of 5-HT metabolism, however the role of other neurotransmitters in the process cannot be neglected, particularly because moclobemide inhibits deamination of NE and DA in the central nervous system [6].

Attention and memory improving effect of moclobemide was also confirmed in clinical studies [24, 32], however, various researches observed different degrees of this effect [2, 11, 36].

The results of our studies showed that chronic stress increased plasma corticosterone concentration in rats, and moclobemide could counteract this effect. According to Burnstein et al. [4], the release of corticosterone is enhanced during stress, and, subsequently, as a result of counterregulatory mechanism high blood level of corticosterone decreases the synthesis of corticotrophin (CRF) and, subsequently, the level of glucocorticoids in the central nervous system is decreased as well.

It is uncertain whether such a regulatory mechanism is also viable in humans as there are no data available on autoregulation of glucocorticoid receptors in the central nervous system in humans. However, there are grounds to believe that these mechanisms of action are similar. In major depression, Gormley et al. [13] found increased level of plasma cortisol, and decreased density of glucocorticoid receptors on lymphocytes.

Antidepressants, such as tianeptine or moclobemide, by eliminating the symptoms of depression, can restore normal functioning of the HPA hormonal axis (they inhibit the rise in ACTH [5, 31] and plasma corticosterone levels in rats and prevent the decrease in the density of type I glucocorticoid receptors [8, 26, 28]). Serotonin may play a role in the effects of stress on the nerve cells. Tianeptine which is known to enhance 5-HT uptake, as well as moclobemide which influences monoamine me-

tabolism (including 5-HT metabolism) prevent the occurrence of behavioral effects induced by stress [27]. These findings suggest that the synaptic availability of 5-HT is involved in the mechanism leading to stress-induced dendritic remodelling [23, 26].

An important area of the brain which may play some role in the etiology of depression and schizophrenia is the hippocampus [25, 28], the structure which participates in the cognitive processes (e.g. memory) connected with the limbic system [9]. Stress may have a detrimental effect on the hippocampus [37]. Chronic restraint stress causes significant dendritic atrophy of CA₃ pyramidal neurons [20, 21]. In the course of post-traumatic-stress disorder (PTSD), a decrease in the hippocampus size has been observed by neuroimaging [12].

Atrophy and dysfunction of the human hippocampus is a feature of aging in some individuals, and this dysfunction predicts subsequent dementia. There is reason to believe that adrenal glucocorticoids may contribute to these changes since the elevations of glucocorticoids level in Cushing's syndrome and during normal aging are associated with atrophy of the entire hippocampal formation in humans and are linked to deficits in short-term verbal memory [26].

It is a well known fact that severe stress results in the release of endogenous stress-dependent neurohormones, i.e. adrenaline and noradrenaline [42]. In our studies, we found out that chronic stress leads to a rise in DA, DOPAC, and 5-HT concentration in the rat hippocampus without changing the levels of 5-HIAA and NE. Moclobemide prevents the changes in neurotransmitter metabolism induced by stress.

Similar results have been observed by Miura et al. [30]. During forced swimming test a typical behavioral change in mice was observed, and biochemical analyses of the brain revealed significant changes in the monoamine levels. Stress increased the levels of DA, 5-HT and their metabolites. Moclobemide significantly improved performance in the forced swimming test and it could prevent the changes in the turnover of NE, DA and 5-HT induced by stress.

The results suggest that moclobemide may improve the behavioral changes induced by chronic stress through its effect on monoamine metabolism. In consequence, moclobemide improves memory impaired by stress. It is also possible that moclobemide has a modulatory effect on stress-induced

neurotransmitter changes, thus protecting against memory impairment. Our results also suggest that the role of HPA axis and hippocampus may be in the future one of the most important areas in the pathophysiology of affective disorders and other dementive illnesses.

REFERENCES

1. Abraham G.E.: Handbook of Radioimmunoassay ED. Abreham. New York, 1997, 591–656.
2. Amado-Boccaro I., Gougoulis N., Poinier-Littre M.F., Galinowski A., Loo H.: Effects of antidepressants on cognitive function. *Encéphale*, 1994, 20, 65–77.
3. Anisman H., Zacharko R.M.: Pharmacological biochemical and behavioral analyses of depression: animal models. In: *Animal Models of Depression*. Eds. Koob G.F., Ehlers C.L., Kupfer D.J., Birkhauser, Boston, 1989, 204–238.
4. Burnstein K.L., Bellingham D.L., Jewell C.M., Powell-Olivier F.E., Cidlowski J.A.: Autoregulation of glucocorticoid receptor gene expression. *Steroids*, 1991, 56, 52–58.
5. Conrad C.D., Galea L.A., Kuroda Y., McEwen B.S.: Chronic stress impairs rat spatial memory in the Y maze, and this effect is blocked by tianeptine pretreatment. *Behav. Neurosci.*, 1996, 110, 1321–1334.
6. Da Prada M., Zurcher G., Wiuttrich I., Haefely W.E.: The cheese effect and a new reversible MAO-A inhibitors. On tyramine, food beverages and moclobemide. *J. Neural Transm.*, 1988, 26, 31–56.
7. Delbende C., Contesse V., Moncaer E., Kamoun A., Vandry H.: The novel antidepressant: tianeptine, reduces stress-evoked stimulation of the hypothalamo-pituitary-adrenal axis. *Eur. J. Pharmacol.*, 1991, 202, 391–396.
8. Delbende C., Tranchand-Bunel D., Tarozzo G., Grino M., Oliver C., Mocaer E., Vandry H.: Effect of chronic treatment with the antidepressant tianeptine on the hypothalamo-pituitary-adrenal axis. *Eur. J. Pharmacol.*, 1994, 251, 245–251.
9. Eichenbaum H., Oto T.: The hippocampus – what does it do? *Behav. Neural Biol.*, 1992, 57, 2–36.
10. Eroglu L., Guven O.: The effects of moclobemide on the yohimbine-induced anxiogenic action in the elevated plus-maze. *Pharmacol. Res.*, 1998, 37, 137–142.
11. Fairweather D.B., Kerr J.S., Hindmarch I.: The effect of moclobemide on psychomotor performance and cognitive function. *Int. Clin. Psychopharmacol.*, 1993, 8, 43–47.
12. Friedman M.J.: Posttraumatic stress disorder. *J. Clin. Psychiat.*, 1997, 58, 33–36.
13. Gormley G.J., Lowy M., Reder A.T., Hospenhorn V.D., Antel J.P., Metzger H.Y.: Glucocorticoid receptors in depression: relationship to the dexamethasone suppression test. *Amer. J. Psychiat.*, 1995, 142, 1278–1286.
14. Haefely W., Burkard P., Cesura A., Colzi A., Kettler R., Lorez H.P., Martin J.R., Moreau J.L., Richards J.G., Schaffner R., Scherschlicht R., Sepinwall J., Da Prada M.: Pharmacology of moclobemide. *Clin. Neuropharmacol.*, 1993, 16, S8–S18.
15. Katz R.J., Roth K.A., Carroll S.J.: Acute and chronic stress effects on open field activity in the rat: implication for model of depression. *Neurosci. Biobehav. Rev.*, 1982, 5, 247–251.
16. Katz R.J., Sibel A.: Animal model of depression: tests of three structurally and pharmacologically novel antidepressant compounds. *Pharmacol. Biochem. Behav.*, 1982, 16, 973–977.
17. Leonard B.E.: The amine hypothesis of depression: a reassessment. In: *Biochemical and Pharmacological Aspects of Depression*. Eds. Tipton K.F., Youdim M.B.H., Taylor & Francis, London, 1989, 25–49.
18. Liebowitz M.R., Schneier F., Gitow A., Feerick I.: Reversible monoamine oxidase-A inhibitors in social phobia. *Clin. Neuropsychopharmacol.*, 1993, 16, S83–S88.
19. Luine V.N., Villegas M., Martinez C., McEwen B.S.: Repeated stress causes reversible impairments of spatial memory performance. *Brain Res.*, 1994, 639, 167–170.
20. Magarinos A.M., Deslandes A., McEwen B.S.: Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *Eur. J. Pharmacol.*, 1999, 371, 113–122.
21. Magarinos A.M., McEwen B.S.: Stress-induced atrophy of apical dendrites of hippocampal CA₃c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience*, 1995, 69, 89–98.
22. Magnusson O., Nusson L.B., Westerlund D.: Simultaneous determination of dopamine, DOPAC and homovanillic acid. Direct injection of supernatants from brain tissue homogenates in a liquid chromatography – electrochemical detection system. *J. Chromatogr.*, 1980, 221, 234–237.
23. Marinesco S., Poncet L., Debilly G., Jouvet M., Cesuglio R.: Effects of tianeptine, sertraline and clomipramine on brain serotonin metabolism: a voltammetric approach in the rat. *Brain. Res.*, 1996, 736, 82–90.
24. Mashkovskii M.D., Andrejeva N.T., Parshin V.A., Galovina S.M.: The antiamnestic properties of antidepressants. *Farmakol. Toksikol.*, 1991 54, 4–5.
25. McEwen B.S.: Stress and the hippocampus. An update on current knowledge. *Presse Medicale*, 1991, 20, 1801–1806.
26. McEwen B.S., Conrad C.D., Kuroda Y., Frankfurt M., Magarinos A.M., McKittrick C.: Prevention of stress-induced morphological and cognitive consequences. *Eur. Neuropsychopharmacology*, 1997, 7, S323–S328.
27. McEwen B., Frankfurt M., Kuroda Y.: Effect of tianeptine in the consequence of stress in rats. *Neuropsychopharmacology*, 1994, 4, 10–23.

28. McEwen B.S., Gould E.A., Sakai R.R.: The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *Brit. J. Psychiat.*, 1992, 160, 18–23.
29. McKittrick C.R., Blanchard D.C., Blanchard R.J., McEwen B.S., Sakai R.R.: Serotonin receptor binding in a colony model of chronic social stress. *Biol. Psychiat.*, 1995, 37, 383–393.
30. Miura H., Naoi M., Nakahara D., Ohta T., Nogatsu T.: Effects of moclobemide on forced-swimming stress and brain monoamine levels in mice. *Pharmacol. Biochem. Behav.*, 1996, 53, 469–475.
31. Murphy J.M., Olivier D.C., Sobol A.M., Monson R.R., Leighton A.H.: Diagnosis and outcome of depression and anxiety in a general population. *Psychol. Med.*, 1986, 16, 117–126.
32. Nair N.P.V., Ahmed S.K., Ng Ying Kin M.M.K.: Reversible and selective inhibitors of monoamine oxidase A in the treatment of depressed elderly patients. *Acta Psych. Scand.*, 1995, 91, 28–35.
33. Nowakowska E., Chodera A., Kus K., Rybakowski J.: Anxiolytic and memory improving effects of moclobemide. *Arzneim.-Forsch.-Drug Res.*, 1998, 48, 625–628.
34. Nowakowska E., Chodera A., Rybakowski J., Kus K.: Anxiolytic and memory improving activity of fluoxetine. *Pol. J. Pharmacol.*, 1996, 48, 255–260.
35. Przegaliński E, Budziszewska B, Grochmal A.: Effect of adenosine analogues on plasma corticosterone concentration in rats. *Acta Endocrinol.*, 1992, 127, 471–475.
36. Roth M., Mountjoy C.Q., Amrein R.: Moclobemide in elderly patients with cognitive decline and depression. *Brit. J. Psychiat.*, 1996, 168, 149–157.
37. Sapolsky R.: Stress, the aging brain and the mechanism of neuron death. In: *Aging Brain and the Mechanisms of Neuron Death*, MIT, 1992, 423.
38. Versiani M., Nardi A.E., Mundim F.D., Alves A.B., Liebowitz M.R., Amrein R.: Pharmacotherapy of social phobia. A controlled study with moclobemide and phenelzine. *Brit. J. Psychiat.*, 1992, 161, 353–360.
39. Watanabe Y., Gould E., McEwen B.S.: Stress induces atrophy of apical dendrites of hippocampus CA3 pyramidal neurons. *Brain Res.*, 1992, 588, 341–344.
40. Wesnes K.A., Simpon P.M., Christmas L., Anand R., Mc Clelland G.R.: The effect of moclobemide on cognition. *J. Neural Transm.*, 1989, 28, 91–102.
41. Willner P., Muscat R., Papp M.: Chronic mild stress-induced anhedonia, a realistic animal model of depression. *Neurosci. Biobehav. Rev.*, 1992, 16, 525–534.
42. Zhang X., Kindel G.H., Wulfert E., Hanin I.: Effects of immobilization stress on hippocampal monoamine release: modification by mivazerol, a new α_2 -adrenoreceptor agonist. *Neuropharmacology*, 1992, 34, 166–1672.

Received: March 9, 2001; in revised form: April 30, 2001.