ENHANCING EFFECT OF MIRTAZAPINE ON COGNITIVE FUNCTIONS ASSOCIATED WITH PREFRONTAL CORTEX IN PATIENTS WITH RECURRENT DEPRESSION

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MIRTAZAPIN HATÁSA A KOGNITÍV TÜNETEKRE DEPRESSZIÓS BETEGEK PREFRONTÁLIS CORTEXÉN KERESZTÜL

A mirtazapin hatás hipotézisét vizsgálták depressziós betegek kognitív funkcióján, a prefrontális cortex aktivitásváltozásán keresztül. Depressziós betegek 6 hónapon át kaptak mirtazapint, neuropszichológiai tesztekkel a 3. és a 6. hónap után történtek a mérések (Wisconsin Card Sorting Test, N-back Test, TMT és Stroop teszt). Az akut depressziós epizódban mindegyik tesztben szignifikáns javulás jelentkezett.Mindezt a 3 és 6 hónapos gyógykezelés után is észlelték, egészséges önkéntesekkel történtek összehasonlítások.
A mirtazapin a depressziós betegek kognitív tüneteinél szignifikáns javulást okoz, közvetlen összefüggésben a prefrontális cortexre gyakorolt hatással.

KULCSSZAVAK: mirtazapin, kognitív funkciók, prefrontális cortex, depresszió

SUMMARY

Introduction. We put forward a hypothesis that a therapeutic administration of mirtazapine to depressed patients, due to pharmacological profile of the drug, could enhance cognitive functions associated with prefrontal cortex activity.
Methods. The study was performed on depressed patients receiving mirtazapine for the period of 6 months. Neuropsychological assessments after 3 and 6 months of treatment were performed by the Wisconsin Card Sorting Test, N-back test, TMT and Stroop tests.
Results. During acute depressive episode, a significant impairment on all neuropsychological tests was evident. Substantial improvement in performance has been noted after 3 and 6 months of mirtazapine treatment, and, after 6 months, a majority of the investigated patients achieved the results within the range of matched healthy control subjects. Improvement on neuropsychological tests after treatment with mirtazapine showed no correlation with the degree of amelioration of depression.
Discussion. Mirtazapine may exert a favorable influence on cognitive functions associated with prefrontal cortex in depressed patients. The lack of direct correlation with improvement of depressive symptoms suggests that mirtazapine may possess specific pro-cognitive properties.

KEYWORDS: mirtazapine, cognitive functions, prefrontal cortex, depression

INTRODUCTION

Cognitive deficits reflecting disturbance of prefrontal cortex activity have been reported in depressed patients, especially during acute episode (1,4,5,8,19,20). Christopher and MacDonald (6) postulated that depression affects the allocation of attention and all elements of working memory. These abnormalities result in an impairment of performance on neuropsychological tests assessing executive functions such as planning, problem solving and cognitive control. The f-MRI data during the performance of N-back test obtained by Harvey et al (13) indicate that depression may impair cognitive capacity of depressed patients necessitating a recruitment of more brain resources compared to healthy subjects during cognitive task.

Various neurotransmitters, mainly dopamine and norepinephrine modulate the activity of prefrontal cortex and related cognitive functions (10). Mirtazapine is a novel antidepressant drug with a unique pharmacological profile (Nonadrenergic and Specific Serotoninergic Antidepressant). The drug increases noradrenergic and serotoninergic neurotransmission and blocks serotonin receptors 5-HT2 and 5-HT3, exerting no effect on cholinergic system. Pharmacological properties of mirtazapine such as alpha2 receptor blockade and 5HT1A receptor activation could favorably influence the activity of prefrontal cortex. Marcus et al. (18) showed that alpha2 receptors blockade enhances cortical glutamatergic and dopaminergic D1 neurotransmission. Nakayama et al. (21) observed an increase of dopamine release in prefrontal cortex by 5HT1A receptors activation with concomitant improvement of working memory after treatment with mirtazapine.

We put forward a hypothesis that a therapeutic administration of mirtazapine to depressed patients, beside of antidepressant effect, could enhance cognitive functions associated with prefrontal cortex activity. To this aim, we did the assessment of the effect of mirtazapine used for treatment of depressed patients on selected cognitive functions, including tests of working memory, associated with the activity of prefrontal cortex.

METHODS

Subjects

The study was performed on depressed patients receiving mirtazapine treatment for the period of 6 months. All patients were diagnosed as major depressive episode, according to DSM-IV (11), and as moderate or severe depressive episode, single or recurrent, according to ICD-10 (15) (code F32 or F33). In 12 patients, the first depressive episode was diagnosed. In the remaining 59 patients, the number of depressive episodes ranged between 2-12, and the duration of illness was 1-30 years (mean 7±6 years).

Psychometric assessment

For the assessment of the intensity of depressed symptoms the 17-item Hamilton Depression Rating Scale (HDRS) was used (12). Baseline intensity of depression in patients studied, as measured with this scale ranged between 17-32 (mean 24±4) points.

Neuropsychological assessment

1. *The Wisconsin Card Sorting Test* (WCST), which is a standard test used to assess working memory and executive functions. The computer version of WCST designed by Heaton (14) was used in this research. Following domains of WCST were measured, reflecting various aspects of cognitive functions:
   a) The percentage of perseverative errors (WCST-P): inability to change the reaction due to ignorance of relevant stimuli
   b) The percentage of non-perseverative errors (WCST-NP): attention inability to avoid distraction
   c) The number of correctly completed categories (WCST-CC): ability to utilize new information and previous experiences
   d) The percentage of conceptual level responses (WCST-%CONC): ability of conceptual thinking
   e) The set to the first category (WCST-1st CAT): ability to formulate a logical conception
2. *The N-back test.* The test assesses visual working memory and also visuospatial attention, coordination and reaction time. Numbers 2, 4, 6, 8, are presented on the computer screen with duration 1.8 seconds. In 0-back task, which is the control condition, subject is asked to press button corresponding to the current number presented on the computer screen. This part of the test is assessing an ability to perform this kind of task. In 1-back test subject is asked to press button marked with a number seen one presentation before, consequently in 2-back condition – two presentations before. In this version (V1.06.1) according to Coppola, 25 numbers are presented (7). The mean reaction time (N-back time) and percent of correct reactions (N-back %CORR) were assessed. The mean reaction time measures vigilance and selective attention in complex situation and correct reactions reflect the ability of visuospatial working memory and executive control. In this study, 1-back tasks of this test were used.
3. Trail Making Test A&B. The test assessing psychomotor speed (part A) and spatial working memory (part B) (23).
4. The Stroop Color Word Intereference Test for evaluation of verbal abilities (part A) and verbal working memory (part B) (25). The per-

formance of Stroop B is mostly connected with the activity of anterior cingulate cortex.

PROCEDURE

Mirtazapine was administered in daily dose of 30-60 (mean 39.5±11.0) mg. Psychometric and neuropsychological assessments were made before, and after 3 and 6 months of treatment. Seventy-one patients were initially recruited. Nine patients dropped out from the study within 3 months and 2 patients within the next 3 months. Therefore, the final analysis for the effect of mirtazapine on cognitive functions was done on 60 patients (19 male, 41 female), aged 18-67 (mean 46±12) years. For comparison, the neuropsychological data of 30 healthy subjects, matched for gender and age with depressed patients were used.

Statistics

The ANOVA Friedman Test was used to compare the results in all three points: baseline, and after 3 and 6 months. The correlations between variables were calculated by Spearman correlation test. Non-parametric Mann-Whitney test was employed for the comparison of two groups.

RESULTS

Demographic characteristics of 71 investigated patients and 30 healthy controls and the results on HDRS scale in 71 patients with depression at baseline are presented in Table 1. As seen in the table, patients and controls were appropriately matched as to age, gender and education.

In Table 2, the baseline data, and the effects of mirtazapine on cognitive functions in 60 depressed patients after 3 and 6 months are shown. At baseline, a significant impairment on all cognitive functions compared to healthy control subjects was evident in depressed patients, with 42-100% of these patients obtained results below one standard deviation of matched controls. Hundred percent of depressive patients were outside this cut-off point on WCST perseverative errors, mostly connected with prefrontal impairment, and on TMT A, connected with psychomotor slowing, while 95% of patients were impaired on both parts on N-back test.

Substantial improvement in performance on neuropsychological tests was noted after 3 and 6 months. After 6 months of treatment, a substantial proportion (57-83%) of investigated patients achieved the results within the range of healthy control subjects (mean + one standard deviation). Eighty-three percent of patients were within this normal spectrum for the results of TMT B, and 75% for WCST-1st category. A moderate proportion of normal results was obtained for tests, where the results had been the most impaired at baseline, i.e., for WCST-P (60%) and TMT A (57%).

In Table 3, correlation between results of neuropsychological test at baseline, and clinical factors and intensity of depression is shown.

A number of significant correlations were obtained between the factors such as age, duration of illness and number of depressive episodes, and the results of neuropsychological tests. Higher age, longer duration of illness and higher number of depressive episodes positively correlated with worse performance on such tests as WCST-P, WCST-CC, WCST% conc, N-back correct, TMT-A and TMT-B. In addition, worse performance on N-back reaction time correlated with age and the number of episodes, and worse performance on Stroop A – with age and duration of illness. The only correlation with the intensity of depression was that of TMT-B performance.

Treatment with mirtazapine resulted in a significant improvement of depression symptoms. The mean intensity of depression was after 3 months 9±4 points (range 3-24), and after 6 months -6±2 points (range 2-12). Twenty-two patients (36%) achieved remission (HDRS≤7 p) after 3 months of treatment, and 49 (82%) after 6 months. The dose of the drug was correlated with the level of improvement on depressed symptoms after 3 months of treatment ($r = 0.33$; $p<0.01$).

Improvement of performance on neuropsychological tests after 3 and 6 months of treatment with mirtazapine showed no correlation with the level of amelioration of depression. In Table 4, a percentage of improvement in neuropsychological tests after 6 months of treatment in groups divided according to age, number of episodes and the dose of mirtazapine is presented.

Better improvement in WCST-NP was obtained in patients with lower age and lower number of episodes. Otherwise, no significant differences were found.

DISCUSSION

The main finding of the study is showing a remarkable effect of mirtazapine on cognitive func-

Table 1
The baseline characteristic of 71 investigated patients with unipolar depression and healthy controls

	Unipolar depression patients N=71	Healthy controls N=30
Age (years) (range, mean±SD)	18-67 (44±12)	19-67 (44±12)
Sex	23 male, 48 female	10 male, 20 female
Education (years)(range, mean±SD)	8-17 (13.2±3.2)	8-18 (13.5±2.4)
HDRS (range, mean±SD)	17-32 (23.7±4.2)	–
Duration of the illness (range, mean±SD)	2-30 (7.0±6.3)	–
Number of episodes (range, mean±SD)	1-12 (3.9±2.1)	–
The daily dose of mirtazapine (range, mean±SD)	30-60 (39.5±11.0)	–

Table 2. The results of neuropsychological tests in 60 investigated patients with recurrent depression at baseline and after 3 and 6 months of treatment with mirtazapine (The values are given as means±SD)

	Healthy controls	Unipolar depression		
	N=30	BaselineN=60	3 monthsN=60	6 monthsN=60
WCST				
% PE	6.4±1.7	18.5±9.1## (100)	10.2±4.9*##	8.4±5.2*## (40)
% N-PE	8.4±2.2	16.7±8.1 ## (75)	10.8±5.9*##	10.0±5.1*(28)
CC (no)	5.9±0.3	4.4±1.9 ## (58)	5.1±1.5*#	5.3±1.0*# (42)
% conc	80.6±5.2	59.9±17.9## (72)	74.3±14.9*	74.9±14.4*(37)
1st cat. (no)	11.4±0.9	23.4±30.5## (42)	14.0±7.8*	13.9±7.7*(25)
N-back				
Correct (%)	98.3±3.4	61.3±21.0## (95)	86.1±13.8*##	91.9±10.8*##
Reaction time (sec)	657.6±232.5	1201.9±319.9## (95)	860.1±195.0*##	(35)754.7±180.8*#(27)
TMT (sec)				
part A	26.6±7.2	42.1±9.9## (100)	32.4±7.0*##	31.6±5.8*## (43)
part B	52.5±11.6	98.3±50.2##(82)	63.3±27.0*	56.4±15.0* (17)
Stroop (sec)				
part A	23.3±6.1	31.8±8.3## (67)	27.2±4.8*##	27.3±5.6*## (38)
part B	52.8±7.7	88.8±27.7## (85)	67.4±16.9*##	63.7±14.3*## (35)

The figures in parentheses at baseline and after 6 months of treatment stand for the percentages of results of depressed patients worse than 1SD of healthy control subjects.
Difference vs healthy controls significant #p<0.05; ##p<0.001
Difference vs baseline significant , * p< 0.001 ANOVA Friedman Test.

Table 3. Correlation between the results of neuropsychological test at baseline and clinical factors and intensity of depression

	Age	Duration of illness	Number of episodes	Intensity of depression (HAMD)
WCST P	0.39**	0.58**	0.54**	0.02
WCST NP	-0.02	-0.03	-0.04	0.08
WCST CC	-0.26*	-0.45**	-0.43**	0.02
WCST % con	-0.38**	-0.48**	-0.53**	-0.01
WCST 1st cat	0.15	0.18	0.21	-0.01
N-back correct	-0.39**	-0.42**	-0.50**	-0.17
N-back reaction	0.23*	0.20	0.25*	0.21
TMT-A	0.31**	0.42**	0.37**	0.21
TMT-B	0.43**	0.56**	0.47**	0.31**
Stroop A	0.30*	0.36**	0.21	0.07
Strop B	0.20	0.13	0.04	0.08

Table 4. The mean percentage of improvement in neuropsychological tests and clinical factors after 6 months of treatment

	Age		Number of episodes		Dose of mirtazapine	
	<50 n=32	≥50 n=28	1-2 n=15	≥3 n=45	≤30 n=31	>30 n=29
WCST P	41±21	45±24	44±20	42±23	39±23	47±21
WCST NP	56±18	30±29*	54±26	41±27*	47±24	41±30
WCST CC	35±89	57±79	31±79	49±86	51±93	37±75
WCST % con	33±55	42±61	28±34	40±63	40±72	34±37
WCST 1st cat	4±35	18±42	13±31	9±42	1±45	20±31
N-back %correct	53±53	93±100	48±53	80±87	56±64	89±93
N-back reaction time	37±14	4(?)±173	40±12	15±137	34±13	8±171
TMT-A	23±18	23±13	25±14	22±17	26±15	18±17
TMT-B	35±16	39±16	35±13	38±17	41±15	33±16
Stroop A	11±20	13±16	17±16	10±19	15±17	8±19
Strop B	24±15	25±23	29±11	23±21	29±15	20±22

Difference between groups significant *p<0.05, Mann-Whitney test

tions associated with prefrontal cortex activity in depressed patients. Such effect has been significant after 3 months of treatment and in some domains showed further increase after 6 months. Another finding was that such effect was not significantly correlated with the antidepressant effect of the drug.

In our study, a significant impairment during acute depressive episode was found on all subtests of WCST, N-back as well as on TMT and Stroop tests. Nearly all patients had the results below cut-off point lower that 1SD of healthy subjects for such prefrontal tests as WCST-perseverative errors and both parts of N-back test. The results of neuropsychological tests obtained in depressed patients at baseline may confirm the data of other authors pointing to a significant impairment of cognitive functions, including those connected with prefrontal cortex activity, in depression (1,5, 19,6,20,22). Such results have been supported by neuroimaging finding showing impaired function of prefrontal cortex in depressed patients (2,4,13).

Correlation analysis of our baseline data revealed worse results on most neuropsychological parameters studied in patients with higher age, longer duration of illness and with higher number of depressive episodes. This is in agreement with data of some authors (3, 9) but not with others (26). The exception in our study for age, duration of illness, and number of episodes was WCST-NP, which mostly measures the parameter of attention. Interestingly, no relationship was found between the quality of performance on most tests and the intensity of depression. The only significant correlation between depression was obtained with TMT-B. This may suggest that the impairment of cognitive flexibility measured by this test may make an element of clinical picture of depression. Our results did not confirm those of Merriam et al. (20) who found a correlation between the intensity of depression and some domains of WCST. However, the mean intensity of depression in patients studied by theirs was significantly lower than in our group (17-item HDRS 17±6).

Treatment with mirtazapine resulted in an improvement on all neuropsychological tests studied. About 2/3 of patients who had obtained at baseline pathological results in WCST-P, and both parts of N-back test, fell into normal values after 6 month of mirtazapine treatment. The analysis of relationship of improvement with clinical factors did not reveal significant differences, except for WCST-NP. The amelioration on this test was weaker in older patients and in those with higher number of illness episodes.

The improvement of neuropsychological tests did not show any correlation with the degree of amelioration of depression. Interestingly, the highest percentage of patients in normal range of results was observed for TMT-B, the only parameter which correlated with the intensity of depression at baseline. Similarly, in our study of mirtazapine in fibromyalgia, a therapeutic effect of the drug on main fibromyalgia symptoms was not directly connected with the antidepressant one (24).

As suggested previously, the beneficial effect of mirtazapine on prefrontal cortex activity may be connected with the pharmacological profile of the drug, especially with alpha2 receptors blockade (18) and activation of 5HT1A receptors (21). A potential mechanism for ameliorating frontal functions after mirtazapine may be also connected with inhibition of cortisol secretion by this drug (16). Increased cortisol levels may impair cognition, also associated with prefrontal cortex (17).

In summary, the results of our study strongly suggest that mirtazapine exerts a favorable influence on cognitive functions, including those associated with prefrontal cortex activity, in depressed patients. The lack of direct correlation between improvement of cognitive functions and that of depressive symptoms indicates that mirtazapine may possess specific pro-cognitive properties.

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