

**COMPARATIVE ANALYSIS OF INFLUENCE SPIROCYCLIC
DERIVATIVES OF OXINDOLE AND VITA-MELATONIN ON CENTRAL
NERVOUS SYSTEM**

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The article deals with the comparative analysis of the influence and vita-melatonin on indicators of the functional activity of the central nervous system by the test "open field." It has been established the compounds under study exceeds activity vita-melatonin. The new compound activates the motion and exploratory activity and does not increase the level of emotion and autonomic responses.

Key words: spirocyclic oxindole derivative, vita-melatonin, functional indicators of central nervous system

The promising area of the modern medicine is the use of medicines 'melatonin'. The Melatonin is the main coordinator of the biological rhythms, but like some other biogenic amines has neurotransmitter functions - providing postsynaptic membrane excitability and is involved in conducting nerve impulses. Melatonin reveals powerful antiradical, anti-hypoxic and membrane-protective properties. In the latest decade, some researches have proved the activity of melatonin in the treatment of certain groups of cancer patients [4,5,6]. The main feature of the melatonin pharmacological profile is its dependence on the daily lighting. 30 mg of melatonin is synthesized per day in the body of the average adult, but its concentration in serum at night is 30 times more than daily content, the maximum activity of melatonin is recorded at 2 p.m.. It has been established that the antioxidant, anti-hypoxic and other effects of the melatonin are reduced during the daytime period to 2-4 times comparing to the dark time period [7].

For today the recommended indications for prescribing the melatonin is the prevention and treatment of circadian rhythm disorders "sleep-wake" and sleep disorders, as well as application to enhance mental and physical performance, simplification of the stress reactions and depression. So we can say that an indication for the use of drugs melatonin has gone beyond chronopharmacological treatment and covered a wide range of patients with disorders of psycho-emotional sphere [8].

The high efficiency of the melatonin and, at the same time, it has a wide therapeutic index, a small number of adverse reactions, which has made it attractive to the drug therapy for many diseases, but significant restrictions on prescribing the drug is especially its pharmacokinetic profile (fast inactivation when illuminated). The previously mentioned things have predetermined the relevance search of the melatoninlike drugs whose effectiveness is not dependent on the significant changes of daily biorhythms. The scientists of the National University of Pharmacy have synthesized a new pharmacy combinatorial library of the compounds of structural analogues of the melatonin derivatives – the spirocyclic oxindole derivatives. At the Department of Organic Chemistry, National University of Pharmacy, Redkin R.G., PhD, led by prof. Shemchuk L.A. it has been sensitized some series of original compounds spirocyclic oxindole derivative, including the defined leader in anti-hypoxic effect - under the designation compound 77 [3]. In the previous studies its significant antidepressant and anxiolytic activity has been found [2].

The aim of this work is conducting a comparative analysis of the impact on the performance of the central nervous system of : spirocyclic oxindole derivative and vita-melatonin.

Materials and methods. To study the dose-dependent effect of compound 77 and comparison products – according to the chemical structure of the core molecule – the vita-melatonin, we have conducted the test of "open field" for male mice, by which we have examined the locomotor activity, conduct research and autonomic emotional responses [1]. The evaluation criterion was the number of crossed squares, uprights, looking into the holes, fecal bolus, urinations and grooming episodes for 5 min. observation. The animals were divided into the following groups: intact control (n = ten), the introduction of compound 77 in the 0.5 mg / kg (n = ten), the introduction of compound 77 in the 5 mg / kg of the drug compared vita-dose melatonin in 0.5 mg / kg, the introduction of vita-melatonin 5 mg / kg. The compound 77 and vita-melatonin were administered for 3 days, but the last time 40 minutes before the experiment. For the statistical analysis we have used Student's "t-criteria" by using the programme of the statistical analysis StatPlus 2009.

Results and discussion. The results of the research are presented in the Table 1, additional analysis of the locomotion research activity and autonomic responses have been shown in Pic. 1 - 2.

Putting the compound 77 at a dose of 0.5 mg / kg does not significantly have an impact on the studied parameters of the central nervous system that are within the physiological norm. It may be noted a slight tendency to increase in animal locomotion research activity and a slight decrease in autonomic responses (Pic. 1-2).

The results of the study have revealed that the administration of the compound 77 at a dose of 5 mg / kg for at least three days, has a positive effect on the functional performance of the central nervous system (Table 1). The tested compound has significantly increased the locomotor activity of the animals in terms of crossed squares ($62,3 \pm 2,93$ vs. $49,8 \pm 3,36$ in the intact control group), also this index is by 18% more than the activity of animals which got the vita-melatonin in two doses of 0.5 mg / kg and 5 mg / kg ($50,7 \pm 2,76$ and $52,1 \pm 2,75$ respectively).

TABLE 1. The effect of the test compound 77 and vita-melatonin on performance testing "open field" in mice under conditions of three times administration (n = 10)

№	Group	Показники (за 5 хв.)					
		Number of squares crossed	Counters	Inspection of the holes	Grooming (emotional reactionin)	Bolus	Urinations
1	Intact control	49.8±3.36	12.0±1.21	21.4±6.88	0.90±0.27 (0÷2)	1.20±0.44 (0÷4)	0.40±0.16 (0÷1)
2	Compound 77, 0.5 mg/kg	55.5±2.99	15.0±1.82	21.6±1.94	0.90±0.23 (0÷2)	0.50±0.17 (0÷1)	0.40±0.15 (0÷1)
3	Compound 77, 5 mg/kg	62.3±2.93 * # \$	16.6±1.35 *	27.6±2.27	0.70±0.21 # \$ (0÷2)	0.30±0.15 (0÷1)	0.10±0.10 # \$ (0÷1)
4	Vita-melatonin 0.5 mg/kg	50.7±2.76	13.7±1.71	18.8±2.31	1.60±0.31 (0÷4)	1.50±0.41 (0÷3)	0.70±0.15 (0÷1)
5	Vita-melatonin 5 mg/kg	52.1±2.75	13.2±1.36	20.0±2.46	1.80±0.29 * (1÷4)	1.70±0.43 (0÷4)	0.80±0.20 (0÷2)

Notes

1. * Significant differences to the intact control, p <0.05;
2. # Significant differences to the vita-melatonin at a dose of 0.5 mg / kg, p <0.05;
3. \$ Significant differences to the vita-melatonin at a dose of 5 mg / kg, p <0.05.Примітки:

summation of researching locomotor activity

intact control (n = 10)

the compound 77, 0.5 mg/kg (n=10)

the compound 77, 5 mg/kg (n=10)

vita-melatonin, 0.5 mg/kg (n=10)

vita-melatonin, 5 mg/kg (n=10)

Notes: 1. * Significant differences to the intact control, $p < 0.05$;

2. # Significant differences to the vita-melatonin at a dose of 0.5 mg / kg, $p < 0.05$;

3. # Significant differences to the vita-melatonin at a dose of 5 mg / kg, $p < 0.05$.

Picture 1. Aggregation index of the locomotor activity of mice under the influence of compounds 77 and vita-melatonin in the test "open field"

summation of researching locomotor activity

intact control (n = 10)

the compound 77, 0.5 mg/kg (n=10)

the compound 77, 5 mg/kg (n=10)

vita-melatonin, 0.5 mg/kg (n=10)

vita-melatonin, 5 mg/kg (n=10)

Notes: 1. * Significant differences to the intact control, $p < 0.05$;

2. # Significant differences to the vita-melatonin at a dose of 0.5 mg / kg, $p < 0.05$;

3. # Significant differences to the vita-melatonin at a dose of 5 mg / kg, $p < 0.05$. Fig .

2. Aggregation index of autonomic responses of mice under the influence of compounds 77 and vita-melatonin in the test "open field"

More expressed differences of the activation of the locomotor retrieval of the animals under the influence of the compound 77 at a dose of 5 mg / kg, have been detected by the aggregation rate (Pic. 1). It should be noted that the emotional background of the animals has not been significantly changed under the conditions of the essential input of the compound 77 at a dose of 5 mg / kg.

A positive feature of the new compounds are likely redundancy of the autonomic responses (by 56% under the conditions of the administration of the compound 77 in a dose of 0.5 mg / kg and 75% at a dose of 5 mg / kg ($p < 0.05$) relative to intact control) which means that while there is the increase of the motor and research activity, there is the redundancy of the level of anxiety in the experimental animals.

The Vita-melatonin in doses of 0.5 mg / kg and 5 mg / kg has almost no effect on the locomotor activity and researching animals' behavior (Table 1, Pic. 1), but from the point of view of the psycho-emotional sphere we have established some negative reactions, for instance, during the vita-melatonin administration at a dose of 5 mg / kg, a number of grooming acts has been increased twice, comparing to the intact control group (Table 1). This is confirmed by the literature as for the possibility of heightened irritability, aggressiveness, anxiety symptoms as side effects while taking the medicine. The increase of the anxiety levels is also verified according to the lowest vegetative functioning component of the neural system during the ingestion (Pic. 2).

Conclusions

According to the results of the carried comparative analysis of the influence to the indicators of the central nervous system according to the test "open field" have been found that 4.3'-spiro [(2-amino-3-ciano-4.5-digidropirano [3.2-s] chromen -5-on)-5-metil-2'-oxindol] (spirocyclic oxindole derivative), has increased the locomotor performance and researching activity in contrast to the vita-melatonin, and reduced a number of the autonomic responses.

Thus, there has been established the benefits of the new compounds, of the structural analogue of the melatonin, according to the influence on the indicators of the functional activity in the test "open field".

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