УДК 615.225.2:615.015.26 https://doi.org/10.33250/19.01.082

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Study of psycho- and neurotropic effects of modern β-adrenoblockers

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Key words: β-adrenoblockers, central nervous system, psycho- and neurotropic effects

In the structure of morbidity, disorders of the cardiovascular system occupy one of the leading places. Therefore, optimization of pharmacotherapy of cardiovascular diseases is one of the urgent problems of medicine and pharmacology [1, 2]. β-Adrenoblockers (β-ABs) are one of the group of drugs of first choice for therapy and prevention the complications of arterial hypertension, coronary heart disease, tachyarrhythmias and other cardiovascular diseases [3]. Modern β-ABs differ in pharmacodynamic and pharmacokinetic characteristics and are classified according to cardioselectivity, the degree of water and lipophilicity, the presence of internal sympathetic and membrane-stabilizing activity, stability and duration of action, etc. [4].

The main side effects of β-ABs are hypotension, bradyarrhythmias, impaired peripheral blood circulation, bronchoconstriction, hypoglycemia, dyslipidemia, neurological disorders, decreased potency, dyspeptic phenomena, etc. Most of the side effects are inherent primarily to non-selective β-ABs [5, 6].

As is known, β-ABs are divided into lipophilic, hydrophilic and amphophilic according to the degree of solubility. Lipophilic β-ABs (metoprolol, oxprenolol, propranolol, etc.) are almost completely absorbed from the gastrointestinal tract, easily penetrate the blood-brain barrier (BBB) and increase the tone of the vagus nerve, which is associated with the occurrence of central side effects, such as disturbances sleep, general weakness, memory impairment, depression, convulsions, hallucinations, terrible dreams [7, 8]. CNS disorders may result from cellular hypoxia due to poor cardiac output, direct CNS depression caused by sodium channel blockade, or even occur as a result of hypoglycemia. Lipophilic β-ABs have an increased distribution in the brain and, as a rule, cause severe effects on the CNS. Propranolol has the greatest lipophilicity (the coefficient of solubility in lipids is equal to one). This determines its pronounced central side effects. A sufficiently high level of lipophilicity is also characteristic of metoprolol, so it is also able to cause unwanted reactions from the CNS [9, 10].

Hydrophilic β-ABs (for example, atenolol, nadolol, sotalol) are poorly absorbed in the gastrointestinal tract, do not penetrate or poorly penetrate the BBB, and have almost no effect on the central nervous system. These β-ABs are practically devoid of central side effects. But instead, in the annotation, for example, to atenolol, possible unwanted reactions from the central

nervous system are given, as well as information is provided regarding the limitation of activities that require a high speed of mental and physical reactions. Amphophilic β-ABs (for example, bisoprolol, pindolol) dissolve in lipids and water, are able to penetrate the BBB in small amounts and have a moderate effect on the CNS [11–13].

Information regarding the psycho- and neurotropic properties of various β-ABs in various literature sources is quite contradictory and needs to be confirmed based on the results of both preclinical and clinical trials. In addition, the effect of β-ABs on the central nervous system can be considered not only from the point of view of undesirable reactions, but also as additional pharmacological effects of drugs of this group.

The aim of the study was to investigate the specifics of the effects of the widely used cardioselective β_1-ABs atenolol, metoprolol, and bisoprolol on the central nervous system of experimental animals.

Materials and methods. For a comparative evaluation of the spectrum of psycho- and neurotropic properties of atenolol, metoprolol, and bisoprolol, we studied their effects on the behavior of intact rats in the open field, elevated cruciform labyrinth, and rotating rod tests, in accordance with the methodological recommendations for the preclinical study of medicinal products [14].

After taking the initial parameters, the animals of the experimental groups were given the above-mentioned β-AB once intragastrically using a probe: atenolol and metoprolol at a dose of 10.0 mg/kg, bisoprolol at a dose of 0.5 mg/kg. Doses of the studied drugs were calculated for rats according to the formula of Yu. R. Rybolovlev. The study was conducted 30 minutes after the administration of the corresponding drug.

In the open field test, we assessed locomotor and exploratory activity, vegetative accompaniment of emotional reactions under the influence of the studied substances. The evaluation criteria were the number of crossed squares, vertical stands, looking into holes, fecal boluses, urination and grooming in 5 minutes observation. For a comparative assessment of the spectrum of anxiolytic and sedative activity of the selected drugs, we studied their effect on the behavior of intact animals in the test of elevated cruciform labyrinth. This made it possible to assess the influence of the studied substances on the emotional sphere and state of anxiety of intact rats. The test is based on rodents' natural fear of being in open areas and falling from a height. The state of anxiety of the rats was assessed according to the following indicators: the time of the latent period of entering the dark chamber, the time of total stay in the light and dark compartments, the number of transitions from compartment to compartment, the number of fecal boluses and urinations. The effect of drugs on muscle tone and coordination of movements was determined by changes in the time the animals stayed on a rod with a diameter of 2 cm, which rotates at a speed of 10 rpm. compared with a similar indicator before the introduction of the corresponding substance. The retention time on the rod was chosen as the evaluation criterion. Three attemts were performed for each animal.

Pharmacological studies were conducted on 30 rats bred in the vivarium of the Central Research Laboratory of the National University of Pharmacy in accordance with GLP requirements and with the methodological recommendations of the State Expert Center of the Ministry of

Health of Ukraine. Experimental studies were conducted in accordance with the European Union Directive 2010/10/63 EU on animal experiments.

In the case of recording the results in the form of mean ± standard error, the statistical reliability of intergroup differences was calculated according to the Student's t test with Bonferroni correction.

Results and their discussion. As a result of the conducted studies, it was determined that in the open field test, atenolol at a dose of 10 mg/kg contributed to a significant decrease in locomotor activity and suppressed indicators of the emotional state of rats. Atenolol did not affect their research behavior. The drug reliably reduced the sum of all activities by 2.3 times, that is, it revealed a certain depressing effect on the central nervous system of experimental animals (Table 1).

Bisoprolol at a dose of 0.5 mg/kg in the open field test did not affect locomotor activity and exploratory behavior, did not suppress indicators of the emotional state of animals. This drug did not reliably change the sum of all activities, i. e., unlike atenolol, it did not show any effect on the central nervous system of rats (Table 1).

Metoprolol in a dose of 10 mg/kg significantly reduced the locomotor activity of experimental animals. The number of crossed squares against the background of the drug decreased by 2.4 times, the number of vertical racks by 2.3 times. The drug also inhibited the exploratory activity of rats, as evidenced by a significant decrease in the number of examined holes by 3.1 times compared to a similar indicator in the intact control group. Also, the researched drug suppressed indicators of the emotional state of animals, namely, reduced the number of boluses, urination and defecation. Metoprolol reliably reduced the sum of all activities by 2.9 times, that is, it revealed a depressing effect on the central nervous system of rats (Table 1).

In the test of the elevated cruciform labyrinth (Table 2), it was determined that the introduction of atenolol contributed to an increase in the latent period of animals entering the dark compartment (by 216%), the time spent in the light arms of the maze (by 336%), which indicates a decrease in anxiety. The total time the rats spent in the dark compartments of the maze was significantly reduced by 23%. But at the same time, the introduction of the drug did not cause significant changes in the indicators of the vegetative accompaniment of emotional reactions (the number of fecal boluses and urinations). Therefore, it can be stated that atenolol has moderate selective anxiolytic properties (Table 2).

A single administration of bisoprolol did not cause changes in the time of the latent period of rats entering the dark compartment, did not change the time the rats stayed in the light and dark arms of the maze, did not cause reliable changes in the number of fecal boluses and urinations, which indicates that the drug does not have anxiolytic properties. Therefore, it can be stated that bisoprolol in the selected dose does not have a significant effect on the activity of the central nervous system of experimental animals (Table 2).

The use of metoprolol contributed to an increase in the latent period of animals entering the dark compartment (by 267%) and the time spent in the light arms of the maze (by 383%), which indicates a decrease in anxiety. The total time the rats spent in the dark compartments of the maze was significantly reduced by 28%. Administration of the drug helped to reduce the indicators of vegetative

Table 1

Effects of atenolol, bisoprolol and metoprolol on the behavior of intact rats in the open field test (M ± m)

Indicator	Intact control (n = 5)	Atenolol, 10 mg/kg (n = 5)	Intact control (n = 5)	Bisoprolol, 0.5 mg/kg (n = 5)	Intact control (n = 5)	Metoprolol, 10 mg/kg (n = 5)
Number: – crossed squares – vertical racks	 40.75 ± 5.56 4.0 ± 0.58	 17.0 ± 2.06* 1.75 ± 0.25*	 35.30 ± 3.60 6.30 ± 1.50	 39.0 ± 3.90 6.80 ± 0.80	 35.30 ± 4.60 6.30 ± 1.50	 15.40 ± 3.0* 0.60 ± 0.20*
Number of examined holes	3.75 ± 0.66	3.0 ± 0.43	4.30 ± 0.30	3.80 ± 0.20	4.30 ± 1.30	1.40 ± 0.70*
Emotional and autonomic reactions: – grooming – fecal boluses – urination – the sum of indicators	 1.70 ± 0.20 0.75 ± 0.16 2.50 ± 0.50 4.95 ± 0.36	 0.40 ± 0.10* 0 0.75 ± 0.10* 1.90 ± 0.18*	 1.70 ± 0.20 2.0 ± 0.20 6.0 ± 0.40 9.70 ± 1.10	 1.30 ± 0.10 1.80 ± 0.20 6.80 ± 0.70 9.90 ± 1.40	 1.70 ± 0.90 2.0 ± 0.20 6.0 ± 1.30 7.70 ± 1.50	 0.80 ± 0.1* 0.20 ± 0.10* 0.20 ± 0.10* 1.20 ± 0.30*
Sum of all activities	53.45 ± 8.45	23.65 ± 3.26*	55.70 ± 5.10	59.30 ± 3.70	55.70 ± 9.0	19.30 ± 3.70*

*Note, here and on Table 2, 3: *p < 0.05 compared to indicator of corresponding intact control.*

accompaniment of emotional reactions, namely, it reliably reduced the number of fecal boluses and urinations by 3.6 times (Table 2). Therefore, metoprolol has anxiolytic properties and is able to show a certain depressant effect on the central nervous system. The latter confirms the anti-anxiety effect of the drug, revealed in the open field test.

The results obtained indicate that a single administration of atenolol significantly reduced the time spent by the experimental animals on the rotating rod in two out of three attempts. Thus, in the second attempt, the time the rats were kept on the rod decreased by 1.7 times, in the third attempt – by 1.5 times, compared to similar indicators of intact rats. This indicates a significant decrease in the tone of skeletal muscles and deterioration in the coordination of the movements of experimental animals under the influence of atenolol (Table 3).

Bisoprolol, in contrast to atenolol did not reduce the time the experimental rats stayed on the rod, but also reliably increased this indicator in two attempts. Thus, in the first and second attempts, the time the rats were kept on the rod increased by an average of 1.9 times. In the third attempt, the time the animals stayed on the rod increased by 1.3 times, but these changes were not reliable. That is, it can be assumed that bisoprolol is able to increase physical activity and improve coordination of movements of experimental animals. A single administration of metoprolol led to a reduction in the time the animals stayed on the rod in two out of three attempts. Thus, in the second attempt, the time the rats were kept on the rod was significantly reduced by 1.3 times, in the third attempt – by 2.1 times, compared to similar indicators of intact rats. This indicates a significant decrease in the tone of skeletal muscles and deterioration of the coordination of the movements of the experimental animals against the background of the studied drug (Table 3).

So, it was determined that atenolol and metoprolol, unlike bisoprolol, have a moderate depressant effect on the central nervous system, reduce muscle tone, and worsen the coordination of movements of experimental animals. On the other hand, it can be assumed that atenolol and metoprolol have moderate sedative and anxiolytic properties. The data obtained on the psycho- and neurotropic effects of metoprolol fully correspond to the literature data [15]. They can be explained by a sufficiently high level of lipophilicity of the drug. The use of metoprolol and atenolol can have a negative effect on activities that require high speed of mental and physical reactions, making quick decisions (for example, driving vehicles, servicing machines and mechanisms, working at height), therefore, during the treatment period you should refrain from such activities. The results of the study regarding atenolol do not coincide with the data of literary sources [16, 17].

Bisoprolol, unlike atenolol and metoprolol, does not change locomotor activity and exploratory behavior, does not suppress indicators of the emotional state of animals, that is, it does not have a significant effect on the central nervous system of experimental rats. This was confirmed by open field and cross maze tests. A very interesting result was obtained in the rotating rod test. We found out that bisoprolol is able to increase physical activity and improve coordination of movements of experimental animals. These results don't completely coincide with the literature data that bisoprolol is able to penetrate through the BBB in a small amount and have a moderate effect on the central nervous system [18].

Table 2

Effects of atenolol, bisoprolol and metoprolol on the behavior of rats in the test of elevated cruciform labyrinth (M ± m)

Indicator	Intact control (n = 5)	Atenolol, 10 mg/kg (n = 5)	Intact control (n = 5)	Bisoprolol, 0.5 mg/kg (n = 5)	Intact control (n = 5)	Metoprolol, 10 mg/kg (n = 5)
The latent period of entering the dark compartment, s	16.10 ± 2.0	34.75 ± 0.5* (+216%)	2.0 ± 1.0	3.50 ± 1.30	9.0 ± 1.0	24.0 ± 3.30* (+ 267%)
Total time of stay in light compartments, s	21.80 ± 1.50	73.2 ± 4.4* (+336%)	2.0 ± 1.0	8.20 ± 2.60*	27.0 ± 3.10	103.40 ± 14.90* (+ 383%)
Total time of stay in dark compartments, s	278.20 ± 12.60	226.75 ± 10.6* (-23%)	298.0 ± 11.0	291.80 ± 14.50	271.0 ± 11.80	196.60 ± 17.40* (- 28%)
Number of transitions	0.80 ± 0.10	1.9 ± 0.2	0	0.80 ± 1.50	4.20 ± 1.50	7.90 ± 0.60*
Number of fecal boluses and urinations	1.20 ± 0.30	1.80 ± 0.3	0	1.80 ± 0.30	5.10 ± 0.20	1.40 ± 0.40*

Table 3

Effects of atenolol, bisoprolol and metoprolol on muscle tone and motor coordination of rats in rotating rod test (M ± m)

Attempt	Retention time on the rod, s					
	Intact control (n = 5)	Atenolol, 10 mg/kg (n = 5)	Intact control (n = 5)	Bisoprolol, 0.5 mg/kg (n = 5)	Intact control (n = 5)	Metoprolol, 10 mg/kg (n = 5)
First attempt	16.30 ± 2.70	20.30 ± 4.20	23.0 ± 5.90	42.90 ± 6.50*	21.20 ± 3.10	29.25 ± 5.50
Second attempt	38.0 ± 5.20	22.80 ± 3.50*	22.80 ± 6.50	44.30 ± 5.60*	38.0 ± 4.20	28.40 ± 3.60*
Third attempt	40.30 ± 9.40	27.0 ± 4.90*	27.70 ± 3.80	35.20 ± 9.40	40.30 ± 9.40	19.60 ± 2.30*

Thus, we investigated the effect of the drugs on the CNS of intact animals after a single administration. It would be interesting to research the effect of the drugs on the CNS of experimental animals under the conditions of the corresponding model pathology and after repeated administration. In the future, this may become the basis for expanding the pharmacodynamics of the studied drugs.

Conclusions

1. It was shown, that atenolol and metoprolol have moderate sedative and anxiolytic effects in the open field and elevated cruciform labyrinth tests. Bisoprolol, unlike atenolol and metoprolol, does not affect the CNS of experimental animals.
2. In the rotating rod test it was determined, that bisoprolol causes a mild actoprotective effect, significantly increasing the physical endurance of experimental animals.
3. Assumptions regarding the stress-protective properties of atenolol and metoprolol, as well as the actoprotective effect of bisoprolol, require verification and confirmation in further in-depth studies.

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Study of psycho- and neurotropic effects of modern β-adrenoblockers

In the structure of morbidity, disorders of the cardiovascular system occupy one of the leading places. Therefore, optimization of pharmacotherapy of cardiovascular diseases is one of the urgent problems of medicine and pharmacology. β-Adrenoblockers (β-ABs) are widely used in the therapy and prevention of complications of many cardiovascular diseases. The main side effects of β-ABs are hypotension, bradyarrhythmias, impaired peripheral blood circulation, bronchoconstriction, hypoglycemia, dyslipidemia, neurological disorders, decreased potency, dyspeptic phenomena, etc. Information regarding the psycho- and neurotropic properties of β-ABs in various literature sources is quite contradictory and needs to be confirmed based on the results of both preclinical and clinical trials.

The aim of the study was to investigate the specifics of the effects of the widely used cardioselective β_1-ABs atenolol, metoprolol, and bisoprolol on the central nervous system of experimental animals.

For a comparative evaluation of the spectrum of psycho- and neurotropic properties of atenolol, metoprolol, and bisoprolol, we studied their effects on the behavior of intact rats in the open field, elevated cruciform labyrinth, and rotating rod tests.

It was determined that atenolol and metoprolol, unlike bisoprolol, have a moderate depressant effect on the central nervous system, reduce muscle tone, and worsen the coordination of movements of experimental animals. This indicates the ability of drugs to suppress the activity of the central nervous system. The use of metoprolol and atenolol can negatively affect activities that require high speed of mental and physical reactions, quick decision-making. On the other hand, moderate sedative and anxiolytic properties of atenolol and metoprolol can be considered as additional pharmacodynamic possibilities. Bisoprolol is practically devoid of central side effects inherent in β-ABs. It can be assumed that bisoprolol has a mild actoprotective effect. The results obtained do not coincide with the data of the literature.

The pharmacodynamics of modern β-ABs has not yet been definitively studied. Additional data will allow not only to specify the side effects of the drugs and to determine the conditions for their rational use, but will also help to expand the pharmacodynamic capabilities of certain drugs of this group.

Key words: β-adrenoblockers, central nervous system, psycho- and neurotropic effects

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Вивчення психо- та нейротропних ефектів сучасних β-адреноблокаторів

У структурі захворюваності порушення серцево-судинної системи посідають одне з провідних місць. Тому оптимізація фармакотерапії серцево-судинних захворювань є однією з актуальних проблем медицини та фармакології. β-адреноблокатори (β-АБ) широко застосовуються в терапії багатьох кардіоваскулярних захворювань і в профілактиці їхніх ускладнень. Основними побічними ефектами β-АБ є гіпотензія, брадіаритмія, порушення периферичного кровообігу, бронхоконстрикція, гіпоглікемія, дисліпідемія, неврологічні розлади, зниження потенції, диспепсичні явища тощо. Інформація щодо психо- та нейротропних властивостей β-АБ у різних джерелах літератури є достатньо суперечливою та потребує підтвердження за результатами як доклінічних, так і клінічних випробувань.

Мета дослідження – вивчити особливості впливу широко застосовуваних кардіоселективних β-АБ атенололу, метопрололу та бісопрололу на центральну нервову систему (ЦНС) експериментальних тварин.

Для порівняльної оцінки спектра психо- та нейротропних властивостей атенололу, метопрололу та бісопрололу вивчали їхній вплив на поведінку інтактних щурів у тестах відкритого поля, піднесеного хрестоподібного лабіринту та стрижня, що обертається.

Визначено, що атенолол і метопролол, на відміну від бісопрололу, виявляють помірний пригнічувальний вплив на ЦНС, знижують м'язовий тонус, погіршують кординацію рухів експериментальних тварин. Це свідчить про здатність препаратів пригнічувати активність ЦНС. Застосування метопрололу та атенололу може негативно впливати на діяльність, яка вимагає високої швидкості психічних і фізичних реакцій, прийняття швидкого рішення. З іншого боку, помірні седативні й анксіолітичні властивості атенололу та метопрололу можна розглядати як додаткові фармакодинамічні можливості. Бісопролол практично позбавлений центральних побічних ефектів, що притаманні β-АБ. Ми з'ясували, що бісопролол здатний збільшувати фізичну активність і покращувати координацію рухів експериментальних тварин. Можна припустити наявність у бісопрололу м'якої актопротекторної дії. Отримані результати не співпадають з даними літератури.

Фармакодинаміка сучасних β-АБ поки що остаточно не вивчена. Додаткові дані дозволять не тільки конкретизувати побічні ефекти препаратів і визначити умови їхнього раціонального застосування, але й допоможуть розширити фармакодинамічні можливості певних лікарських засобів цієї групи.

Ключові слова: β-адреноблокатори, центральна нервова система, психо- та нейротропні ефекти

Надійшла: 15 жовтня 2024 р.

Прийнята до друку: 19 лютого 2025 р.

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