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Nootropic effect peculirities of β-cyclodextrin clathrate with succinic acid in experiment

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ABSTRACT

In the present study it is shown the data of experimental testing of laboratory animals in universal problem camera in the application chamber CD-SA (clathrate β-cyclodextrin with the succinic acid in the ratio 2:1) in comparison with the alternative drugs (Mexidol and succinic acid). The experimental results showed that by the dose 10 mpg it significantly changes the indices predominantly of the cognitive sphere, expressing nootropic properties. It is shown, that in the raw of the drugs of comparison according to the degree of impact on the cognitive sphere, the effect CD-SA is close to the similar effect of Mexidol. Presumably CD-SA potentially activates the mechanisms of the declarative memory in the laboratory animals in the experiment.

INTRODUCTION

Currently β-cyclodextrin and its numerous derivatives are widely used in physiology and pharmacology [1-7]. They are mainly used as the “containers” of medicinal drugs due to its natural ability to encapsulate different hydrophobic compounds with the formation of inclusion compounds of the “quest–host” type [5-7]. The inclusion compounds are cyclodextrin clathrates with the known pharmacological substance, which display the various bioactivity and attract the definite interest from the practical point of view [8-10].

The inclusion complexes with the succinic acid, medicinal drugs containing the succinic acid are displayed in many experimental and clinical researches. The succinic acid and its derivatives became widely used as means of broad activity spectrum: antihypoxic action, actoprotective, nootropic effect, adaptogenic effect and others [11-14].

This work presents the details on synthesis and experimental trial of the nootropic activity caused by the new chemical compound representing clathrate β-cyclodextrin with the succinic acid in the ratio 2:1 in comparison with the alternative drugs (Mexidol and succinic acid).

MATERIALS AND METHODS

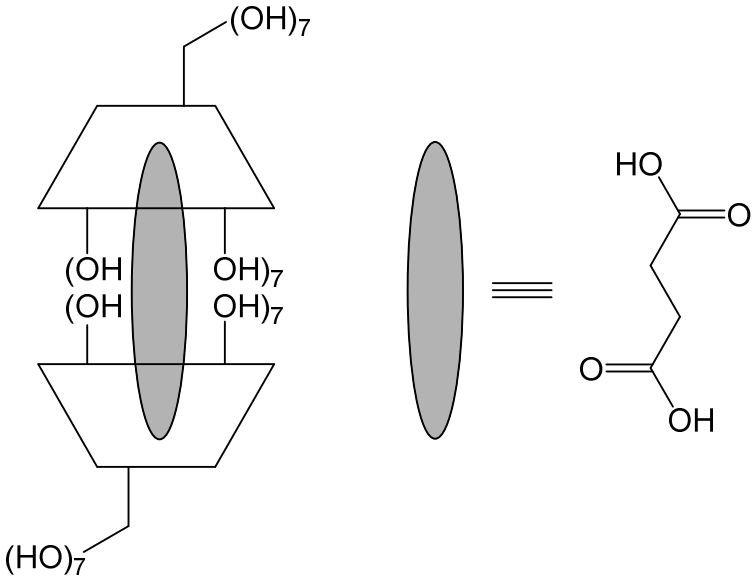
Experiments were carried out with 64 white male rats with the weight of 150-200 g, kept in the standard conditions of the vivarium taking into consideration the principles of humanity, and the plan of the study met conditions of

Helsinki declaration of World Medical Association (WMA) of the latest revision (Edinburg, 2000), with the account of explaining comment to the paragraph 29, which was added by General Assemblée of WMA (Washington, 2002). Before organizing the study all the animals were kept in the standard conditions. The rats were given a full food ration during 10 days before the beginning of the experiment according to the Rules of organizing works using experimental animals (1977).

The experimental animals were subjected to the primary typological selection according to the method [15]. The species belonging to the second behavioral type took part in this set. The measures of the behavioral search activity, registered in the universal problem camera, are susceptible to the influence of the pharmacological substances having the actoprotecting and neurotropic activity [16].

The testing consisted of 2 stages: at the first stage the formation of the instrumental reflex of active avoidance behavior in the problem camera was held; at the second stage the testing itself was carried out during 3 days. During the second stage the characteristics of the motivational-energetic (according to the indicants of search time (ST) and search intensity (SI)) and cognitive spheres (according to the cognitive component (CC)) in accordance to the accepted methods were registered [15]. Additionally the vector of the direction of error paces was analyzed.

The utilized substance (Fig.1) represents the chemical synthesized compound. This compound was received according to the following pattern.



Pic. 1. Graphic formula of clathrate β-cyclodextrin with succinic acid (CD – SA).

A solution of 0.50 g (0.44 mmol) of beta-cyclodextrin in 20 mL of water was heated to 70°C, 0.026 g (0.22 mmol) of succinic acid was added, and the mixture was stirred for 1 h at 70°C. The mixture was cooled to room temperature and slowly evaporated to 1/3 of the initial volume in a desiccator over P_2O_5, and the precipitate was filtered off, washed with water (2×2 mL), and dried under reduced pressure (1 mm) for 4 h at 50°C. Yield 0.28 g (54%), mp 240–242°C (decomp.), R_f 0.41 (Silufol UV-254 plates were used for thin-layer chromatography; eluent: chloroform–methanol, 3:2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: beta-cyclodextrin: 3.20–3.70 m (84H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.45 br.s (14H, 6-OH), 4.79 br.s (14H, 1-H), 5.65 br.s (28H, 2-OH, 3-OH); succinic acid: 2.37 s (4H, CH_2), 12.15 br.s (2H, COOH). Found, %: C 44.40; H 6.05. $C_{88}H_{146}O_{74}$. Calculated, %: C 44.26; H 6.16.

The results of the testing in the problem camera revealed that under the influence of CD-SA the indicator of cognitive sphere mainly changes (fig.2).

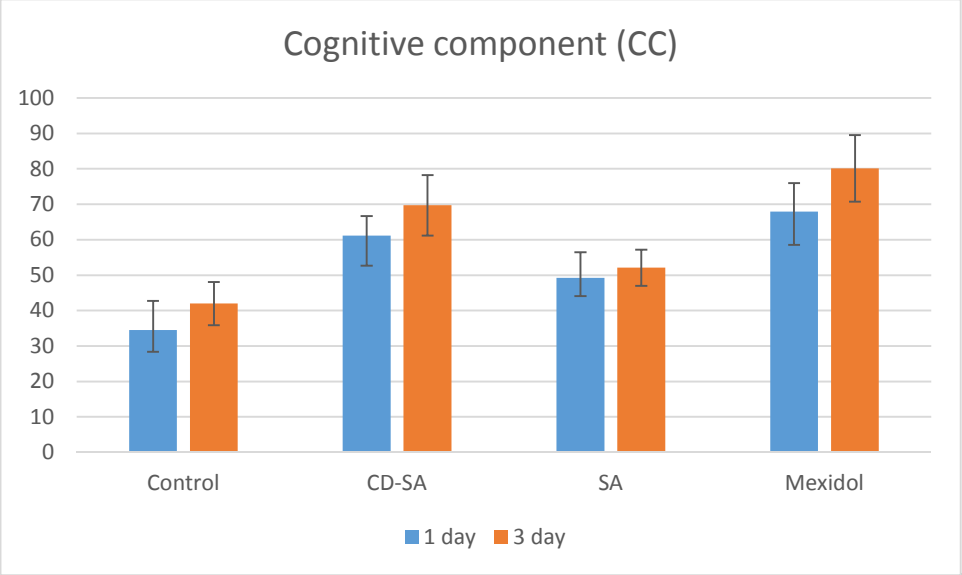


Fig.2. Cognitive component (in %) under the influence of CD-SA and preparations of comparison (SA and Mexidol)

During the first day it increased in 1.8 times ($p<0.05$), during the third day – in 1.7 times ($p<0.05$). It demonstrates the evident nootropic proved by the identical dynamics in the preparations of comparison (SA and Mexidol). In the group with SA the similar effect was observed, but it was less significant. In the group, which got Mexidol, known by its evident secondary nootropic qualities, the CC increase was the highest, but at the same time it was significantly above the measures in the group with CD-SA. The last one proves the high-potency of our new clathrate.

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By the qualitative characteristics of the erroneous actions in the whole one can judge about the cognitive process in the conditions of the highly frustrating situation. Therefore we additionally carried out the analysis of the strategy (vector) of the error paces.

Analyzing the vector of the error paces just as during the first day so during the third day of the testing under the influence of CD-SA, the significant changes were observed (fig.3).

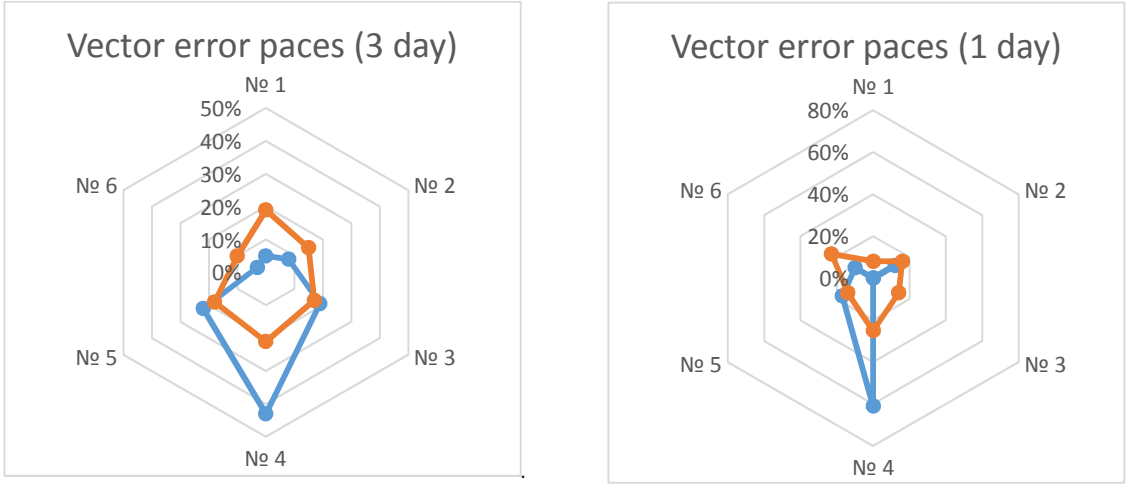


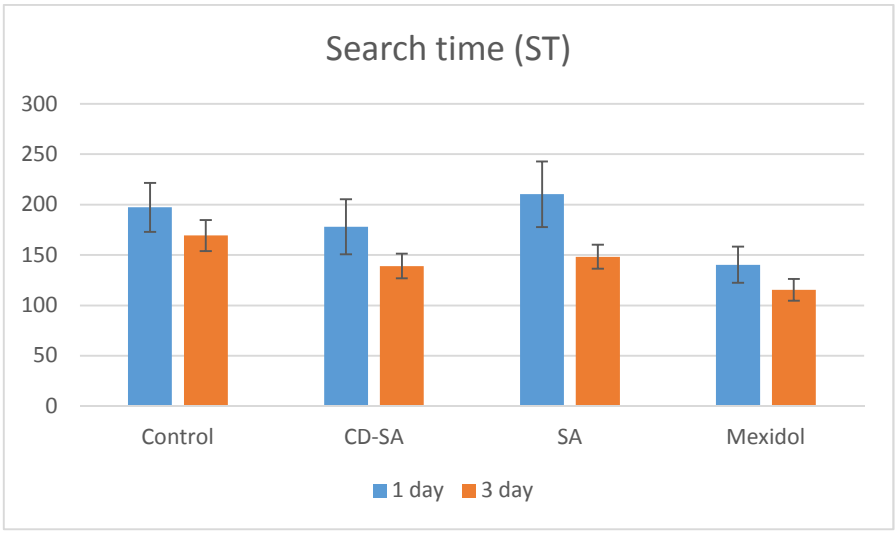
Fig.3. Graphic picture of the error paces in the control and experimental groups under the influence of CD-SA (blue color – control group, red color – experimental group)

Thus, for instance, during the first day of the testing under the influence of CD-AS, the percentage of direction towards the exits № 1, 3 increased to 8 and 14% correspondingly. Attendance of the most popular exit № 4 decreased from 61% (in control) to 25% (in the experimental selection). On the third day of the testing, the error frequency to the most preferable exit № 4 decreased from 43% to 21%, and in the less attended exits (№ 1, 2, 6) increased in 2-3 times.

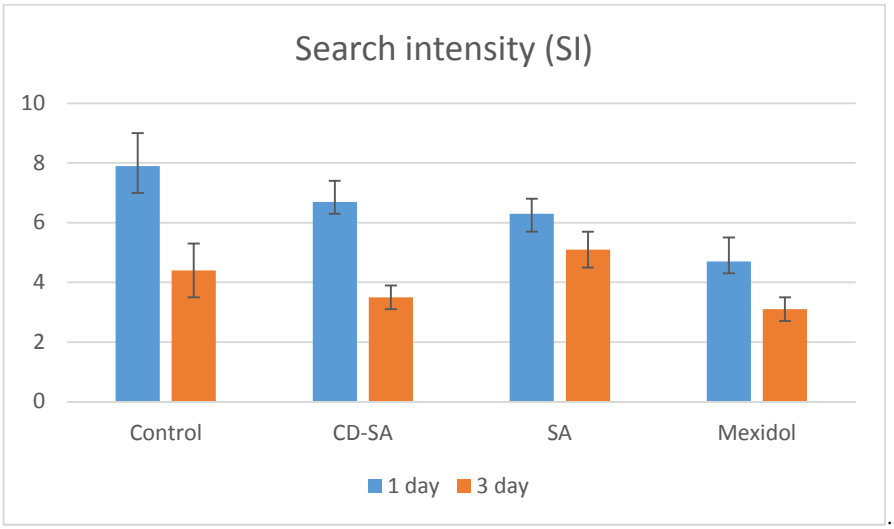
There is a certain “alignment” of the direction of error paces. It is the sign of the positive dynamics in cognitive activity, as the animals began to use widely the test cases. The positive quantities of CC changes in the groups under the influence of the test substance (pic.2) are proved.

In our opinion, in the experimental groups on the background of the working (and dominating in control group) mechanisms of the procedural memory, the declarative memory mechanisms start to work. The last ones as far as they are included lead to vector changing in particular, to its one sidedness, though it’s realized at the cost of error making into other exits, including the exits earlier not used. According to all the observable features we can conclude of the positive influence of CD-AS.

Characterizing the indices of the motivational-energetic sphere (ST, SI), in animals administered CD-SA there were the insignificant dynamics of its positive shift (fig.4a and b).



a



b

Fig.4. Indices of motivational-energetic sphere a) ST and b) SI in control group and under the influence of CD-SA, SA, Mexidol

During the first day ST was down by 9.7%, during the third day – by 17.9% in comparison with control ($p>0.05$). During the first day SI was down by 15.2% and during the third day it was down by 20.5% without the truly

significant difference. The largest shift to the decrease side was observed in the group with Mexidol and SA in its pure form practically didn't influence these indices.

Thus, summarizing the resulting data, it is necessary to note that the new synthesized compound CD-SA predominantly influences the cognitive sphere of the behavior and in a less degree influences the motivational-energetic indices. In our previous works[10] we tested the similar derivative of β-cyclodextrin with the para-amino-benzoic acid and silyl group (CD-PABA-CG), that displayed the opposed action and significantly changed the motivational-energetic characteristics, practically without impact upon the cognitive sphere. Consequently, such a various influence of these compounds reveal the different suppositions for its further practical appliance. We may recommend CD-PABA-CG and perform pre-clinical tests concerning the correction of the physical endurance, working efficiency, speed of muscular reaction and others, CD-SA is recommended to use as the perspective nootropic agent.

It should be noted, that SI decreases insignificantly under the influence of CD-SA. It demonstrates the degree of "fussiness" in the realization of the behavioral act and it serves as a good background for optimization of the cognitive sphere with its metabolic support. The last one is an important factor in the context of gaining the positive behavioral experience by biological species at reaching the final adaptive results with the formation of engrams based on personal experience.

The lower intensity of the discussed effect from the side of SA (in comparison with CD-SA), most probably is concerned with the real existence if its structural-chemical "loneliness". As it was demonstrated in our researches[8-10, 17]and in a few works of other authors[1-7], cyclodextrin is a kind of a reliable "supporter" and sometimes a "defender" in the biophysical processes with the certain drug substances and other substances. These substances chemically form with cyclodextrin the clathrates and conjugates, conducing in some cases achievement of the therapeutic effect in lower doses.

Cyclodextrins, as naturally occurring compound (Schardingerdextrins), most probably possess the evolutionary developed high degree of the affinity to biological environment, for which reason they display the various positive physiological effects. The cyclodextrin frame protects the enclosed drug substance from biodegradation, makes for the increase of solubility and serves its selective delivery to the required place for the required time period [8,9,15,18].

CONCLUSION

1. The compound CD-SA (clathrate β-cyclodextrin with succinic acid in the ratio 2:1) in the dose 10mpg significantly changes the indices predominantly of the cognitive sphere in the universal problem camera in the laboratory animals, having the nootropic impact.
2. In the raw of the drugs of comparison according to the degree of impact on the cognitive sphere, the effect CD-SA is close to the similar effect of Mexidol.
3. CD-SA potentially activates the mechanisms of the declarative memory in the laboratory animals in the experiment.

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