

Short reports

The Effect of Alkylglycerol Ethers on Anxiety

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Abstract: Objective — To evaluate the potential of alkylglycerol ethers (AGEs) for enhancing behavioral models.

Methods — AGEs for the experiment were isolated from the digestive gland of the gonad squid (*Berryteuthis magister*) and purified using conventional methods. The AGE composition was determined by chromatography (GC and GC-MS). Male Wistar rats (15 rats in the experimental group and 15 rats in the control group) were used for behavioral studies. The experimental group received 200 mg/kg AGEs for 22 days. Behavioral studies were conducted using two tests: the Y-maze and the marble burying.

Results — In the Y-maze test, there we revealed no statistically significant differences between animals in the number of errors or overall behavioral activity. There were no significant differences in marble burying test results before AGE treatment and on Day 8 of the experiment. On Day 22 of the experiment, animals in the control group buried more marbles than animals receiving AGEs ($p=0.040$).

Conclusion — The effect of AGEs is more closely related to anxiety, particularly obsessive-compulsive behavior, than to memory. AGEs reduced anxiety levels in rats, thereby improving their adaptation.

Keywords: alkylglycerol ethers, animal behavior, anxiety.

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Introduction

The study of biologically active compounds obtained from marine animals is a rapidly developing field of science, becoming interdisciplinary in nature [1].

Alkylglycerol ethers (AGEs) are precursors of plasmalogens, which are involved in the development of the nervous system and its normal functioning by regulating the release of neurotransmitters, as well as in the mechanisms of socially important neurodegenerative diseases such as Alzheimer's disease [2].

We investigated the effect of AGE administration on animal behavior, hypothesizing that this effect might be evident, as these compounds showed good results in our experiments with acute and chronic stress [3-5].

Methods

AGE preparation

The magister armhook squids (*Berryteuthis magister*) were collected from the Bering Sea. Their digestive gland was frozen at -18 °C. We used all analytical-grade chemical reagents and solvents from Sigma-Aldrich (USA). AGEs were obtained according to the method by Ermolenko et al. [6].

AGE Analysis

The experimental substance contained 95% of chimyl alcohol (16:0 radical) and 5% of batyl alcohol (18:0 radical) by weight. To identify trimethylsilyl derivatives of AGEs (TMS-AGEs), we used GC and GC-MS [7]. The resulting AGE preparation was a white, odorless, free-flowing powder.

Animal treatment

We used male Wistar rats in the study. They were approximately 2–3 months old at the time of the experiment. Rats were maintained in a vivarium under natural light and on a standard diet. Before the experiment, rodents weighed 178 ± 21 g and were weighed every 5–10 days. For 22 days, experimental animals ($n=15$) were force-fed with an aqueous suspension of AGEs at a dose of 200 mg/kg, while 15 control rats were given just water. The volume of administered fluid was approximately 0.5 mL.

At the end of the experiment, rats were anesthetized with isoflurane and euthanized.

Behavioral tests

The marble burying test was performed using nine marbles (2.5 cm in diameter) for 10 minutes. The experimental box measured 45 cm × 24 cm × 21 cm [8].

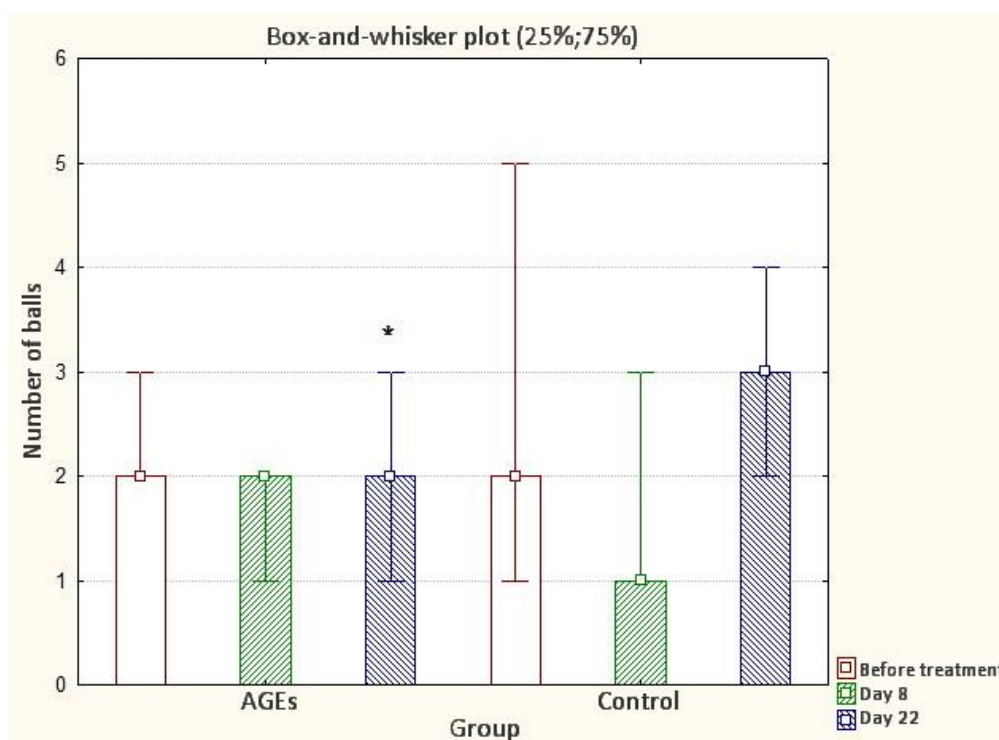


Figure 1. Marble burying test results.

* The difference between the control and experimental groups at the end of the experiment was statistically significant on Day 22 ($p=0.040$).

Table 1. Results of the Y-maze test in rats

Parameter	AGEs group	Control group	Statistics
Number of errors	0.27±0.47 0 (0-0.5)	0.11±0.33 0 (0-0)	Z=0.93; p=0.350**
Number of regular overlapping triplets	6.3±3.1	8.4±1.3	t=2.31; p=0.200*
Total number of selections	11.9±3.6	14.1±2.3	t=2.3; p=0.160*
Spontaneous alternation rate	68.7±14.2	70.4±8.3	t=2.31; p=0.560*

*, Student's t-test; **, Mann-Whitney test.

The Y-maze test measured the number of correct overlapping triplets (alternations), the total number of choices, and the number of errors (repeated choices of the same target) over 5 minutes. The spontaneous alternation rate was then calculated [9].

Statistical analysis

Statistical data were processed using Statistica 10.0 software. Normality of distribution was tested using the Shapiro-Wilk test. Data are presented as median, lower (25%) and upper (75%) quartiles, mean, and standard deviation from the mean. Student's t-test and the Mann-Whitney test were used to compare groups.

Results

AGE administration at the chosen dose had no significant effect on rat body weight.

Differences between groups in the marble burying test were not statistically significant either at the beginning of the experiment or 8 days after the start of AGE administration

([Figure 1](#)). On Day 22 of the experiment, animals in the control group buried more marbles (on average, 3.2 ± 1.5) than animals receiving AGEs (on average, 1.9 ± 1.1), and the difference between the groups became statistically significant ($t=-2.25$; $p=0.040$).

The results of the Y-maze test are presented in [Table 1](#). No significant differences were observed between the control group and rats given AGEs.

See General research design in [Appendix 1](#).

Discussion

Plasmalogens regulate normal neural activity and the entire brain, preventing the development of dementia and neuroinflammation [4]. Taking into account our research on stress [3-5], we therefore, hypothesized that AGEs might improve behavioral patterns.

The Y-maze test has been described for assessing cognitive function [10], but it is also suitable for studying stereotypic behavior in rodents [11].

Rodents exhibit an innate preference for alternating movements when exploring a new environment. A marker of repetitive behavior is an increase in the percentage of animals choosing the same direction in the maze twice. In our study, the number of errors indicating repeated choices of the same arm did not differ statistically significantly between animals force-fed with AGEs and control animals.

The total number of choices reflects the animals' activity in the Y-maze. This activity can be viewed as exploratory behavior or as a desire to find a way out of the maze to avoid a new or potentially dangerous situation. In the general behavioral profile of anxiety, the animals' general motor activity is increased [12].

In our experiment, treatment with AGEs reduced the number of marbles buried by the end of the experiment. The effect observed by the end of the experiment (Day 22) was associated with the accumulation of plasmalogens in cells, the precursors of which are AGEs [3-5].

Results of the marble burying test can be used as an indicator of anxiety. However, the marble burying is more relevant for obsessive-compulsive disorders, as a form of anxious behavior, than for other anxiety states [13]. We view our results as a reduction in repetitive behavior associated with anxiety, which can be considered a favorable sign. The obtained results are preliminary and at this stage do not explain which specific form of anxiety is associated with the observed effect.

In 2024 [14], Jiang R. et al. reported that mice treated with diacyl glyceryl ethers (deep-sea shark liver oil) exhibited reduced anxiety and depressive behavior. Unfortunately, the authors did not take into account the complex component composition of shark liver oil, making it difficult to directly attribute the observed biological effect to AGEs, given that polyunsaturated fatty acids [15], squalene [16], vitamin A [17], and vitamin D [18] have already been confirmed to have anti-anxiety effects. Our approach is unique in that we use pure substances (AGEs), allowing for a more accurate assessment of their individual properties. Hence, we find our approach deserving scientific interest in terms of the potential of AGEs in treating anxiety

Conclusion and prospects

The effect of AGEs is more closely related to anxiety, particularly obsessive-compulsive behavior, than to memory. AGEs reduced anxiety levels in rats and, thus, increased their adaptation. Further research in this area may clarify the role and potential use of AGEs in anxiety mechanisms and further explore their role in neurodegenerative diseases. This opens the possibility of using this substance to reduce anxiety and other socially significant diseases in humans. The production of AGEs from readily available raw materials obtained from commercial fisheries facilitates their widespread use in maintaining and restoring health.

Ethical approval

This study was conducted in accordance with ARRIVE guidelines (<https://arriveguidelines.org>) and the Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council, USA). The animal study protocol was approved by the Ethics Committee of the A.V. Zhirmunsky National Scientific Center for Marine Biology, Far Eastern Branch of the Russian Academy of Sciences (protocol # 04 of July 29, 2022).

AI statement

No artificial intelligence or AI-based tools were used in the preparation of this manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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[Appendix 1](#). General research design

