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The effect of exogenous ganglioside GM1 on the expression of apoptotic genes in the hippocampus in a model of chronic alcohol intoxication

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ABSTRACT

Background. Ganglioside GM1 is of interest as a promising compound with nootropic properties for the correction of damage to the central nervous system, particularly in neurodegenerative processes.

Aim. To study the effect of exogenous ganglioside GM1 on the expression of key apoptosis regulatory genes (caspase-1, caspase-3, *Bcl-2*, *BAX*) in the hippocampus of mice under conditions of chronic alcohol intoxication, which acts as a catalyst for neurodegeneration.

Materials and methods. An experiment was conducted on 40 male BALB/c mice divided into 4 groups: intact control, a chronic alcohol intoxication model (intragastric administration of ethanol according to a stepwise schedule for 47 days), and two groups receiving ethanol in combination with GM1 at doses of 10 and 30 mg/kg. The mRNA levels of target genes in the hippocampus were analyzed using quantitative real-time reverse transcription polymerase chain reaction. Statistical data processing was performed using a two-way ANOVA.

Results. Caspase-1 mRNA levels were non-significantly increased in all ethanol-treated groups. Caspase-3 mRNA levels were significantly ($p < 0.05$) increased only in the GM1 30 mg/kg group compared to the model group. *BAX* mRNA levels remained unchanged. *Bcl-2* gene expression in the control group was statistically significantly different from all experimental groups.

Conclusions. The expected effect of GM1 ganglioside at the transcriptional level, namely protection against neurodegeneration, was not confirmed in this model. The key result was the identification of a potential pro-apoptotic effect of a high dose of GM1 (30 mg/kg), manifested by a statistically significant increase in caspase-3 gene expression.

Keywords: alcohol intoxication, monosialotetrahexosylganglioside, alcohol-induced disorders, hippocampus, apoptosis, ganglioside GM1, neuroprotection, quantitative real-time reverse transcription polymerase chain reaction, mRNA, caspase-1, caspase-3, *BAX, Bcl-2*

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Влияние экзогенного ганглиозида GM1 на экспрессию апоптотических генов в гиппокампе на модели хронической алкогольной интоксикации

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РЕЗЮМЕ

Актуальность. Ганглиозид GM1 представляет интерес как перспективное соединение с ноотропными свойствами для коррекции повреждений центральной нервной системы, в частности при нейродегенеративных процессах.

Цель. Изучить влияние экзогенного ганглиозида GM1 на экспрессию ключевых генов-регуляторов апоптоза (каспаза-1, каспаза-3, *Bcl-2*, *BAX*) в гиппокампе мышей в условиях хронической алкогольной интоксикации, выступающей в роли катализатора нейродегенерации.

Проведен эксперимент на 40 самцах мышей BALB/c, разделенных на четыре группы: интактный контроль, модель хронической алкогольной интоксикации (внутрижелудочное введение этанола по ступенчатой схеме в течение 47 дней) и две группы, получавшие этанол в сочетании с GM1 в дозах 10 и 30 мг/кг. Уровень мРНК целевых генов в гиппокампе анализировали методом количественной полимеразной цепной реакции с обратной транскрипцией в реальном времени. Статистическую обработку данных проводили с использованием двухфакторного дисперсионного анализа (two-way ANOVA).

Результаты. Уровень мРНК каспазы-1 статистически незначимо повышен во всех группах, получавших этанол. Уровень мРНК каспазы-3 статистически значимо ($p < 0,05$) повышен только в группе GM1 30 мг/кг по сравнению с модельной группой. Уровень мРНК гена *BAX* оставался без значимых изменений. Экспрессия гена *Bcl-2* в контрольной группе статистически значимо отличалась от всех опытных групп.

Выводы. В рамках данной модели не подтвержден ожидаемый эффект ганглиозида GM1 на транскрипционном уровне, заключающийся в защите от нейродегенерации. Ключевым результатом служит выявление потенциального проапоптотического действия высокой дозы GM1 (30 мг/кг), проявляющегося в статистически значимом повышении экспрессии гена каспазы-3.

Ключевые слова: алкогольная интоксикация, моносиалотетрагексозилганглиозид, алкоголь-индуцированные нарушения, гиппокамп, апоптоз, ганглиозид GM1, нейропротекция, количественная полимеразная цепная реакция с обратной транскрипцией в реальном времени, мРНК, каспаза-1, каспаза-3, BAX, Bcl-2

Как цитировать

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INTRODUCTION

Exogenous monosialotetrahexosylganglioside (hereinafter ganglioside GM1) represents a promising neuroprotective compound of considerable interest. Being a naturally occurring and one of the most abundant gangliosides in the neuronal membranes of the central nervous system, it is obtained as a pharmaceutical agent through extraction from animal brain tissue [1–3]. Its pharmacological value stems from a broad range of neurotropic effects, chief among which is its neurotrophic action, reflected in the potentiation of signaling cascades involving brain trophic factors [1, 4]. The established neuroprotective potential has driven scientific interest in its application for various neurodegenerative conditions, including Parkinson's and Alzheimer's diseases [5–7]. Given its ability to protect neurons from damage and support their function, ganglioside GM1 is considered in the present study a promising candidate for counteracting toxic injury to the hippocampus. A model of chronic ethanol intoxication was used as a well-characterized pathological insult that leads to persistent cognitive impairment and neurodegeneration. This model allows for the study of mechanisms underlying central nervous system damage, a key feature of which is progressive decline in memory and learning functions associated with degenerative changes in the hippocampus.

Activation of programmed cell death is considered a central event in the pathogenesis of ethanol-induced neuronal injury [8, 9]. Accumulating evidence implicates various forms of apoptosis and pyroptosis in hippocampal degeneration [10–12]. However, the contribution of specific molecular cascades, such as caspase-dependent pathways and the system of mitochondrial apoptosis regulators (Bcl-2, BAX), requires further elucidation, which is necessary for the development of targeted neuroprotective strategies [13–20].

As a natural constituent of neuronal membranes, ganglioside GM1 plays a key role in maintaining neuroplasticity and cellular resistance to apoptosis. Existing evidence supports its capacity to modulate trophic factors and suppress oxidative stress [4, 6]. However, the mechanisms underlying its beneficial effects on apoptotic markers and cognitive function under neurotoxic conditions remain insufficiently understood.

AIM

The aim of the present study was to assess the effect of ganglioside GM1 on the transcriptional activity of genes involved in regulating the mitochondrial apoptotic pathway *(BAX, Bcl-2)* and on caspase activity (caspase-1, caspase-3). These parameters were evaluated in the hippocampus under conditions of ethanol-induced neurotoxicity.

MATERIALS AND METHODS

A total of 40 adult male BALB/c mice weighing 25–30 g were used in the experiment. The animals were housed in a vivarium under standard conditions, including a natural light cycle, a temperature of 20–24 °C, humidity of 50–60%, and free access to water and food. All procedures were performed in accordance with international guidelines and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, and the study protocol was approved by the local ethics committee prior to the initiation of the experiment.

After one week of acclimatization, the animals were randomly assigned to four groups of 10 animals each:

1) the control (intact) group that received physiological saline *per os*;
2) the model group that underwent chronic alcohol intoxication according to the protocol;
3) the GM1 10 mg/kg group (therapeutic, low dose) that received ethanol according to the protocol plus ganglioside GM1 at 10 mg/kg;
4) the GM1 30 mg/kg group (therapeutic, high dose) that received ethanol according to the protocol plus GM1 at 30 mg/kg.

Chronic alcohol intoxication was induced by daily intragastric administration of ethanol (97%, Shanghai Aladdin Reagent Company) using a stepwise regimen over 47 days, with progressively increasing concentrations from 5% to 45% (5% solution for 5 days, 15% for 5 days, 25% for 10 days, 35% for 10 days, and 45% for 17 days). The volume of administered solution was adjusted based on individual body weight.

The ganglioside GM1 preparation (Heilongjiang Harbin Medical University Pharmaceutical Co., Ltd.) was dissolved in physiological saline and administered intraperitoneally at the specified doses throughout the experimental period. The control group received equivalent volumes of physiological saline.

After 47 days, the experiment was terminated early due to pronounced signs of deterioration in animals from the model and GM1 10 mg/kg groups. Euthanasia was performed in accordance with the recommendations of the Federation of European Laboratory Animal Science Associations (FELASA). Following induction of deep anesthesia by intraperitoneal administration of 1% sodium pentobarbital, transcardiac perfusion was performed. First, 20–25 mL of physiological saline was injected through the left ventricle to remove blood, which was drained through an incision in the right atrium. Second, perfusion with 4% paraformaldehyde was performed to fix cerebral tissues.

Quantitative analysis of gene expression was performed using reverse transcription quantitative real-time polymerase chain reaction (hereinafter qRT-PCR). Total

Table 1. Primer pairs for qRT-PCR
Таблица 1. Пары праймеров для qRT-PCR

Праймер / Primer		Последовательность праймера (5'–3') / Primer sequence (5'–3')
Каспаза-3 / Caspase-3	Forward	5'-CAGCCAACCTCAGAGAGACA 3'
	Reverse	5'-GCAGTAGTCGCCTCTGAAGA-3'
Каспаза-1 / Caspase-1	Forward	5'-CTGGGACCCTCAAGTTTTGC-3'
	Reverse	5'-AGATCCTCCAGCAGCAACTT-3'
В-клеточная лимфома-2 / B-cell lymphoma 2	Forward	5'-CTTCAGGGATGGGGTGAACT-3'
	Reverse	5'-GCTGGGGCCATATAGTTCCA-3'
Bcl-2-ассоциированный X белок / Bcl-2-associated X protein	Forward	5'-GAGACACCTGAGCTGACCTT-3'
	Reverse	5'-CCCCAGTTGAAGTTGCCATC-3'
Глицеральдегид-3-фосфатдегидрогеназа / Glyceraldehyde-3-phosphate dehydrogenase	Forward	5'-AAGAAGGTGGTGAAGCAGGC-3'
	Reverse	5'-TCCACCACCCTGTTGCTGTA-3'

RNA was isolated from hippocampal tissue samples of BALB/c mice using TRIzol® reagent (Invitrogen, USA) according to the manufacturer's protocol. cDNA was synthesized using a high-efficiency reverse transcription kit for qRT-PCR (ReverTra Ace® qPCR RT Kit, Toyobo, Japan).

Real-time PCR amplification was carried out on an ABI 7500 Fast Real-Time PCR System (Applied Biosystems, USA) using SYBR® Green Realtime PCR Master Mix (Toyobo, Japan). The amplification protocol consisted of initial denaturation at 95 °C for 5 minutes, followed by 40 amplification cycles of 95 °C for 15 s, 65 °C for 30 s, and 72 °C for 30 s, with subsequent melt curve analysis.

Quantitative analysis was performed using threshold cycle (Ct) values determined by the system with automatic baseline setting. Relative gene expression was calculated using the comparative $2^{-\Delta\Delta Ct}$ method, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as a reference gene. Primer sequences are listed in Table 1.

Statistical analysis was conducted using GraphPad Prism version 6.0e for Macintosh (GraphPad Software, USA). Intergroup differences were assessed using two-way analysis of variance (two-way ANOVA) followed by multiple comparisons. The following pairwise comparisons were made: the control group versus the model group, and the GM1 10 mg/kg and GM1 30 mg/kg groups versus the model group. Results are presented as M±SEM, where M represents the mean and SEM represents the standard error of the mean. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

To assess the effects of ethanol exposure and the potential protective effect of ganglioside GM1 on the expression of genes associated with apoptosis and inflammation in the hippocampus of BALB/c mice, qRT-PCR analysis was performed (n=10 per group). A trend toward an increase in caspase-1 mRNA expression was observed in all groups receiving intragastric ethanol (the model, GM1 10 mg/kg, and GM1 30 mg/kg groups) compared with the control group; however, these differences did not reach statistical significance ($p > 0.05$) (Fig. 1a, Table 2). Caspase-3 expression was significantly increased ($p < 0.05$) only in the GM1 30 mg/kg group compared with the model group, with no significant changes observed in the other experimental groups (Fig. 1b, Table 2). Pro-apoptotic *BAX* expression remained relatively unchanged across all GM1-treated groups, and no statistically significant intergroup differences were observed (Fig. 1c, Table 2). An anomalous change in the expression of the anti-apoptotic gene Bcl-2 was noted: its level in the intact control group differed significantly from that in all other groups exposed to ethanol and the administered GM1 doses (Fig. 1c, Table 2).

Analysis of key gene expression in the mouse hippocampus did not yield a clear picture of the molecular and biochemical processes triggered by ethanol administration and ganglioside GM1 treatment. The most contradictory finding was the statistically significant increase in caspase-3 mRNA levels specifically in the GM1 30 mg/kg group compared with the model group. Caspase-3 is a central effector enzyme that initiates apoptosis. These findings suggest that administration of a high dose of ganglioside GM1 in the setting of chronic alcohol intoxication does not suppress but rather may potentiate apoptotic signals in hippocampal neurons. This unexpected effect requires further investigation, as it contradicts the proposed neuroprotective role of gangliosides.

At the same time, the absence of significant changes in pro-apoptotic *BAX* expression across all groups, together with the anomalous *Bcl-2* expression in the control group, underscores the complexity and nonlinearity of apoptotic pathway regulation in this experimental model. The anomaly in the control group may reflect stress from procedures unrelated to ethanol administration, emphasizing the importance of rigorous control group management.

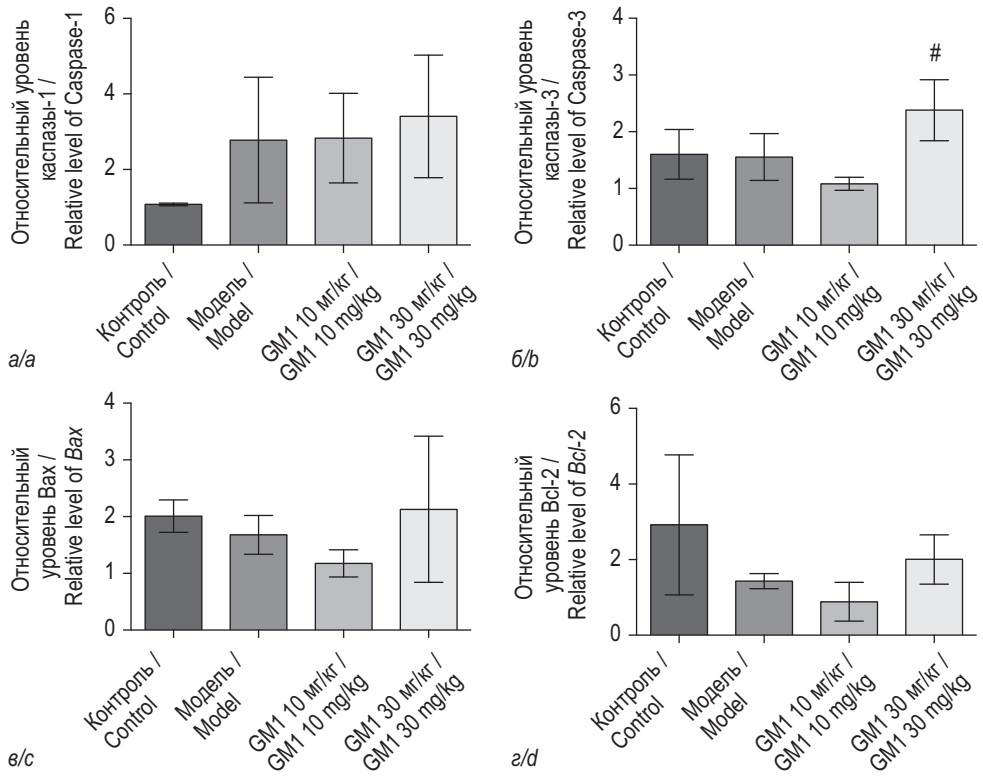

Fig. 1. Evaluation of the activation of apoptotic genes in the hippocampus following intraperitoneal administration of exogenous ganglioside GM1 at different concentrations in a model of long-term ethanol intoxication: *a* — the relative level of caspase-1 was increased in the Model, GM1 10 mg/kg, and GM1 30 mg/kg groups; *b* — the relative expression level of caspase-3 was statistically significantly increased in the GM1 30 mg/kg group; *b* — the relative expression level of *BAX* was not statistically significant; *c* — the relative expression level of *Bcl-2* was not statistically significant. # p=0.0208 (Model vs. GM1 30 mg/kg)

Рис. 1. Оценка активации апоптотических генов в гиппокампе при внутрибрюшном введении экзогенного ганглиозида GM1 в разных концентрациях на модели длительной интоксикации этанолом: *а* — относительный уровень каспазы-1 повышен в граппах «модель», GM1 10 мг/кг и GM1 30 мг/кг; *б* — относительный уровень экспрессии каспазы-3 был статистически значимо повышен в группе GM1 30 мг/кг; *в* — относительный уровень экспрессии *BAX* не показал статистически значимых данных; *г* — относительный уровень экспрессии *Bcl-2* не показал статистически значимых данных. # p=0,0208 («модель» против GM1 30 мг/кг)

Table 2. Intergroup differences in the results of apoptotic gene expression in the qRT-PCR test

Таблица 2. Межгрупповые различия результатов экспрессии апоптотических генов в тесте qRT-PCR

Группы / Groups	M	95% ДИ / 95% CI	p
Каспаза-1 / Caspase-1			
Контроль / Control vs. Модель / Model	–1,703	От –4,271 до 0,8644 From –4,271 to 0,8644	0,2677
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	–0,05339	От –2,371 до 2,264 From –2,371 to 2,264	0,9999
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	–0,6259	От –3,047 до 1,795 From –3,047 to 1,795	0,8796
Каспаза-3 / Caspase-3			
Контроль / Control vs. Модель / Model	0,04697	От –0,7098 до 0,8038 From –0,7098 to 0,8038	0,9979
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,4732	От –0,2100 до 1,156 From –0,2100 to 1,156	0,2355
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	–0,8247	От –1,538 до –0,1112 From –1,538 to –0,1112	0,0208#
Bcl-2			
Контроль / Control vs. Модель / Model	1,489	От –0,5065 до 3,484 From –0,5065 to 3,484	0,1742
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,5465	От –1,206 до 2,299 From –1,206 to 2,299	0,7919
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	–0,5757	От –2,423 до 1,272 From –2,423 to 1,272	0,7922

Окончание табл. 2 / Ending of the Table 2

Группы / Groups	M	95% ДИ / 95% CI	p
BAX			
Контроль / Control vs. Модель / Model	0,3300	От –0,9970 до 1,657 / From –0.9970 to 1.657	0,8911
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,5025	От –0,6953 до 1,700 / From –0.6953 to 1.700	0,6354
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	–0,4514	От –1,702 до 0,7997 / From –1.702 to 0.7997	0,7335

Note: CI — confidence interval; M — mean difference.
Примечание: ДИ — доверительный интервал; M — среднее арифметическое.

With regard to inflammatory markers, the modest increase in caspase-1 mRNA levels observed in all ethanol-treated groups is consistent with evidence that alcohol intoxication can activate the inflammasome and proinflammatory cascades. Nevertheless, the lack of statistical significance suggests that either the effect is modest or a larger sample size is required to detect it. Overall, these findings reveal a complex and somewhat paradoxical effect of ethanol and GM1 on the expression of genes governing apoptosis and inflammation in the hippocampus. The key finding is the absence of a clear neuroprotective effect of GM1 at the transcriptional level in this model, along with a potential pro-apoptotic effect of the high GM1 dose, which warrants further investigation to elucidate the underlying mechanisms. Additional experiments, including assessment of not only mRNA levels but also active forms of the proteins studied, as well as histological analysis, are needed to clarify the overall picture.

CONCLUSIONS

1. When evaluating the effect of ganglioside GM1 on the transcriptional activity of key apoptosis-related genes in the mouse hippocampus under conditions of ethanol-induced neurotoxicity, the expected suppressive effect on the expression of the studied markers was not observed. mRNA levels of the pro-apoptotic gene BAX and the anti-apoptotic gene Bcl-2 did not undergo significant changes. Similarly, caspase-1 gene expression showed only a statistically non-significant trend toward an increase.

2.The key finding was the identification of a potential pro-apoptotic effect of the high dose of ganglioside GM1 (30 mg/kg), which was manifested as a statistically significant increase in mRNA levels of caspase-3, a central effector of apoptosis.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Эксперименты с животными проводили в соответствии с международными правилами (Директивой 2010/63/EU Европейского парламента и Совета Европейского союза от 22 сентября 2010 года по охране животных, используемых в научных целях).

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