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POLYPRENOLS EXTRACT SUPPLEMENTATION MODULATES SCOPOLAMINE-INDUCED NON-SPATIAL AND SPATIAL MEMORY IMPAIRMENTS IN RATS

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The present study was created to assess the effects of chronic polyprenols extract administration (1.0, 5.0 and 10.0 mg/kg, orally, once daily, 14 days) in a scopolamine-induced amnesia. The experimental model of amnesia was created by scopolamine (1.0 mg/kg, s.c.) injection once daily, 14 days. Memory performance was evaluated using the passive avoidance and the Morris water maze tests and the spontaneous locomotor activity was assessed using the open field test. Moreover, we tested acetylcholinesterase (AChE) activity in the brain of the rats with scopolamine-induced amnesia. The polyprenols extract treatment at dose of 1.0 mg/kg significantly ameliorated the impaired cognitive performance induced by scopolamine injection in the rats. The polyprenols extract treatment at dose of 1.0 mg/kg significantly increased locomotor activity, rearing and grooming events and so significantly reversed the behavioral impairments in the rats with scopolamine-induced amnesia in the open field test. Biochemical data showed that polyprenols extract treatment at dose of 1.0 mg/kg significantly decreased and completely restored AChE activity in the brain of the rats with scopolamine-induced amnesia. The results of the present study suggest that chronic polyprenols extract treatment results in memory-enhancing effects of the rats in the passive avoidance test and Morris water maze in an animal model of scopolamine-induced amnesia.

Keywords: Acetylcholinesterase; Polyprenols extract; Learning; Memory; Scopolamine.

Introduction

Alzheimer's disease (AD) is severe neurodegenerative disorder associated with aging and the primary cause of dementia (1). The main behavioral symptoms of AD are the loss of memory and cognition (2). Pathogenesis of AD is very highly complicated. Numerous *in vitro* and *in vivo* experiments have shown that the decreased functional activity of cholinergic neurons in the brain structures involved in cognitive processes such as neocortex, amygdala and nucleus basalis magnocellularis is responsible for AD (3,4). Pathological hallmarks of AD lead to strong decreasing of forebrain cholinergic neurons and reducing in acetylcholine (ACh) levels can arise profound cognitive deficits (5,6). A number of studies on experimental animal models of AD have shown that, both anticholinergic drugs and lesions of the nucleus basalis

of Meynert impairs learning or memory processes in different cognitive-related paradigms such as passive avoidance and Morris water maze tests (7,8). Different drugs created for the AD pharmacoherapy usually act by counteracting the acetylcholine deficit, and are employed to enhance the ACh level in the brain (9). Such treatments stimulating acetylcholine esterase (AChE) efflux markedly improve retention performance in the behavioral paradigms (10,11).

The National Institute of Health suggests, if the current situation continues, there will be more than 8.5 million AD patients by the year 2030 in USA alone (12). Nowadays, there is no specific cure for dementia of AD type (13,14). In this case, alternative pharmacologic treatments might reduce the symptoms of cognitive deteriorations and prevent AD development (15). This has led to the creation and production of beneficial alternative therapies for AD, particularly, phytotherapy with plant drugs. There have been promising developments in the field of plant preparations as sources for new therapies for AD (16,17).

We supposed that polyprenols can be such herbal substance for treatment of AD (18). Polyprenols are plant substances isolated from the neutral fraction of an extract of spruce needles and belongs to the group of polyprenols or isoprenoid alcohols (19,20). It is well-known that polyprenols are multifunctional agents for the prophylactic cancer therapy, liver pathology, cardiovascular diseases, and cognitive impairments (21,22).

We designed the present study to determine the possible cognitive effects of polyprenols extract on memory impairments induced by scopolamine injection. Muscarinic acetylcholinergic receptor antagonists are well-known to impair cognitive-related functions of the brain, and such deteriorations can be observed with the nonselective antagonist, scopolamine. Therefore, scopolamine is often used as an amnestic agent in experimental animal models of memory deficits (23), and it also inhibits central cholinergic neuronal activity (24). The degeneration of basal forebrain cholinergic neurons is associated with impaired cholinergic neurotransmission, induced by hyperactivity of AChE (24). Enhanced AChE activity reduces the ACh level in the brain, which can result in memory impairments (25).

In the present study, we investigated the effects of chronic polyprenols extract treatment on cognitive functions such as spatial and non-spatial learning and memory processes using a rat model of scopolamine-induced amnesia.

Experimental

Male Wistar line albino rats from the special biocollection (Koltushi, St. Petersburg, Russia) weighing 180–200 g each, were used in the present study. All rats were allocated in groups and were allowed to accommodate for one week in the animal house at I.P. Pavlov Institute of Physiology, of the Russian Academy of Sciences, before subjecting them to behavioral testing and pharmacological treatments. They were provided with a standard pellet diet and were given water ad libitum. The animals were kept at a temperature of 23∘C ± 2∘C and a 12 h light/dark cycle as well as a constant relative humidity (50% ± 10%) during all experimental sessions. throughout the experimental period. Total number of animals used in this study was 150 at the beginning of the behavioral experiments. The present study was approved by the Ethical Committee for Animal Research, I.P. Pavlov Institute of Physiology of the Russian Academy of Sciences. All experiments were conducted in accordance with the Guide for Care and Use of Laboratory Animals, published by the National Institute of Health (National Research Council, publication No. 85–23, revised in 1996, and the Animal Welfare Assurance Renewal for the I.P. Pavlov Institute of Physiology, approved by the Scientific Research Committee of the Institute (protocol 1095/1 from June 25, 2012).

Treatments

Scopolamine hydrobromide was purchased from Sigma-Aldrich (MO, USA). It was dissolved in saline and subcutaneously (s.c.) injected in a dose of 1.0 mg/kg, once daily for 14

consecutive days (26). Polyprenols extract was isolated from the green verdure of Picea abies (L.) Karst as previously described (18). The purified polyprenols extract is administered daily at three different doses (1.0, 5.0 or 10.0 mg/kg b.w., orally). All solutions were freshly prepared before each experimental series. All preparations were administered in a volume of 0.1 ml. The rats in the control group received physiological saline. Polyprenols extract, and solvent were administered for 14 days. All behavioral tests were carried out 1 hour after the last injection of scopolamine.

Experimental groups

After adaptation for one week, all male rats were divided randomly into five groups with 10 rats in each group. The first group was served as a control, males received the physiological saline daily (control/solvent). The other group was of male rats with scopolamine-induced amnesia, received the scopolamine daily (rats/scopolamine). The next groups consisted of male rats with scopolamine-induced amnesia treated with polyprenols extract at doses 1.0, 5.0 and 10.0 mg/kg b.w., p.o., daily (rats/polyprenols extract 1.0 mg/kg, rats/polyprenols extract 5.0 mg/kg, rats/polyprenols extract 10.0 mg/kg). Polyprenols extract (1.0, 5.0 or 10.0 mg/kg b.w., orally), or solvent were administered for 14 days once daily before the behavioral tests. The treatment period for animals was 14 days, and at the end of the treatment period (1 h after the last dose of polyprenols extract), all animals were subjected to the passive avoidance paradigm, Morris water maze and the open field test was conducted. During training and testing sessions in all behavioral paradigms the control and experimental groups of rats were also given with encapsulated polyprenols or solvent.

Behavioral tests

All behavioral experiments were performed in a soundproof and air-regulated special room, to which animals were habituated at least 30 min before each training and testing sessions.

Passive avoidance test

Passive avoidance test was carried out using a shuttle box apparatus (18). The apparatus consisted of a lighted and dark compartment with a grid floor. This test was performed for each rat during the 3 days. The step-through latency for animals was recorded on third day. If the animals remained in the lighted box for a 3 min testing period, the maximum score of 180 s was accepted.

Morris water maze

Apparatus is a circular water pool (120 cm in diameter and 60 cm in height) with constant clues external to the maze for spatial orientation of the rats (18). The water was made opaque by adding milk to prevent animals from seeing the submerged platform. The water temperature was kept at 24-26∘C during the whole experiment. An invisible platform (10 cm in diameter and 10 cm in height) providing the only escape from water was placed 2.0 cm below the water surface. The location of the platform remained the same throughout the training period. The pool was located in a test room with a video camera fixed at the top. Six training trials per day were carried out with an inter-trial time period of 2 min. Results of six training trials were collected to obtain a single representative value. Animals that found the platform were allowed to remain on the platform for 30 s and were then returned to the home cage during the inter-trial time period. Animals that did not find the platform within 120 s

were softly guided to the platform for 30 s at the end of the trial. After completion of daily training, the animals were returned to their cages for rest.

Open field test

The open field test (OFT) was performed as previously described by Fedotova and co-workers (18). The apparatus is a square platform (80.0 cm × 80.0 cm; wall height 36.0 cm) with 16 equal squares of 19.5 cm × 19.5 cm. The OFT apparatus was illuminated by a light source of 60 Lux. A video camera fixed at the top. The spontaneous locomotor activity, grooming, and rearing were measured in all experimental and control groups for a 5-min period in the OFT.

Biochemical assay

Estimation of acetylcholinesterase activity

Biochemical assessment was performed on the whole brains of rats selected from each group. Brains were immediately removed, weighed and transferred to a glass homogenizer and homogenized in ice-cold normal saline with a mass ratio of 10% (w/v) with centrifugation at 3000 rpm for 10 min at 4∘C. AChE activity was assessed using commercially available kit (Abcam ab 138871, China). The sensitivity of the kit was 3.0 mU/ml. All the procedures of the AChE activity kit were conducted following the manufacturer's instruction manual.

Statistical analysis

Data were expressed as mean ± S.E.M.. Comparisons between means were performed using one–way analysis of variance (ANOVA) followed by LSD test. Results of behavioral experiments were analyzed using Kruskal–Wallis non-parametric one way ANOVA followed by Dunn's multiple comparisons test. A probability level of less than 0.05 was postulated as significant in all types of statistical tests. Statistical analysis was performed using SPSS software 11.5 version.

Polyprenols extract administration modulates scopolamine induced-memory impairments of rats in the passive avoidance test

Scopolamine caused a profound decrease of the PAR latency which was tested for 24 h after foot shock application in the rats as compared to the control rats ([$F(5,32) = 7.4$, $p<0.05$, Table 1). After polyprenols extract supplementation (1.0 mg/kg, s.c.) the latency of PAR was significantly increased in the rats with scopolamine-induced amnesia as compared to the rats with scopolamine-induced amnesia ($p<0.05$, Table 1). However, the value of PAR latency in the rats with scopolamine-induced amnesia treated was significantly decreased as compared to the control male rats (group 1). Treatment with polyprenols extract supplementation at doses of 5.0 and 10.0 mg/kg per os failed to modify the latency of PAR in the rats with scopolamine-induced amnesia as compared to the rats with scopolamine-induced amnesia ($p<0.05$, Table 1).

Table 1

Latency of passive avoidance response of the rats treated with scopolamine after chronic polyprenols extract administration

Groups	Latency of PAR, sec
Control	180,0 ± 0,6
Scopolamine	4,0 ± 0,4*
Scopolamine + polyprenols extract 1.0 mg/kg	16,0 ± 0,2* **
Scopolamine + polyprenols extract 5.0 mg/kg	4,6 ± 0,4*
Scopolamine + polyprenols extract 10.0 mg/kg	5,2 ± 0,2*

* – P < 0.05 versus the control group, ** – P < 0.05 versus to the rats with scopolamine-induced amnesia. The data are expressed as mean ± SD; n = 10 in each group.

Polyprenols extract administration influences *scopolamine induced-memory impairments of rats in the Morris water maze*

A significant increase of escape latency during the training and testing during the last 4th day of the experimental sessions was observed in the male rats with scopolamine-induced amnesia as compared to the control rats ([F(5,32) = 3.8, p<0.01], Table 2). Polyprenols extract supplementation (1,0 mg/kg, s.c.) caused a significant decrease of escape latency in the rats with scopolamine-induced amnesia as compared to the rats with scopolamine-induced amnesia treated (p<0.05, Table 2). Although, escape latency in the rats with scopolamine-induced amnesia treated with polyprenols extract was higher than that of the control male rats. Treatment with polyprenols extract supplementation at doses of 5.0 and 10.0 mg/kg per os failed to modify the escape latency in the rats with scopolamine-induced amnesia as compared to the rats with scopolamine-induced amnesia (p<0.05, Table 2).

Table 2

Escape latency of the rats treated with scopolamine after chronic polyprenols extract administration in the Morris water maze

Groups	Escape latency on the 4th day of the session, sec	
	Training trial	Testing trial
Control	12,0 ± 0,6	6,3 ± 0,2
Scopolamine	160,0 ± 1,4*	140,0 ± 2,2*
Scopolamine + polyprenols extract 1.0 mg/kg	68,0 ± 3,8* **	45,0 ± 2,4* **

Scopolamine + polyprenols extract 5.0 mg/kg	157,0 ± 2,4*	132,8 ± 4,2*
Scopolamine + polyprenols extract 10.0 mg/kg	155,8 ± 3,6*	142,3 ± 5,2*

* – P < 0.05 versus the control group, ** – P < 0.05 versus to the rats with scopolamine-induced amnesia. The data are expressed as mean ± SD; n = 10 in each group.

Polyprenols extract administration improve scopolamine induced-behavior impairments of rats in the open field test

The male rats with scopolamine-induced amnesia demonstrated a significant decrease of crossing, frequency of rearing and grooming as compared to the control rats ([F(5,32) = 5.44, p<0.05], [F(5,32) = 9.40, p<0.01], [F(5,32) = 19.34, p<0.01], respectively, Table 3). Polyprenols extract supplementation at all doses produced a significant increase of crossing, frequency of rearing and grooming when rats with scopolamine-induced amnesia were compared to the rats treated with scopolamine (p<0.05) (Table 3).

Table 3

Behavioral reactions of the rats treated with scopolamine after chronic polyprenols extract administration in the open field test

Groups	Crossing	Rearing	Grooming
Control	57.3 ± 3.8	11.7 ± 0.8	3.2 ± 0.2
Scopolamine	30.3 ± 2.2*	7.2 ± 0.2*	0.7 ± 0.2*
Scopolamine + polyprenols extract 1.0 mg/kg	67.1 ± 3.2**	12.4 ± 0.2*	2.8± 0.4**
Scopolamine + polyprenols extract 5.0 mg/kg	64.8 ± 1.8**	13.2 ± 0.4**	2.5 ± 0.2**
Scopolamine + polyprenols extract 10.0 mg/kg	57.5 ± 3.6 **	12.8 ± 0.8**	2.8 ± 0.2**

* – P < 0.05 versus the control group, ** – P < 0.05 versus to the rats with scopolamine-induced amnesia. The data are expressed as mean ± SD; n = 10 in each group.

Polyprenols extract administration decreased scopolamine-induced increase of acetylcholinesterase activity in the brain of rats

The obtained results demonstrate that AChE activity in the brain was increased in the rat with scopolamine-induced amnesia ([F(5,32) = 24.4, p<0.05]). In contrast, polyprenols extract at

dose of 1.0 mg/kg suppressed AChE activity in the rats with scopolamine-induced amnesia ($p<0.05$, Table 4).

Table 4

Acetylcholine activity in the brain of the rats treated with scopolamine after chronic polyprenols extract administration

Groups	AChE activity, (U/mg prot)
Control	1,1 ± 0,2
Scopolamine	3,8 ± 0,4*
Scopolamine + polyprenols extract 1.0 mg/kg	1,6 ± 0,2**
Scopolamine + polyprenols extract 5.0 mg/kg	4,6 ± 0,6*
Scopolamine + polyprenols extract 10.0 mg/kg	4,0 ± 0,2*

* – P < 0.05 versus the control group, ** – P < 0.05 versus to the rats with scopolamine-induced amnesia. The data are expressed as mean ± SD; n = 10 in each group.

Other experimental groups were treated with polyprenols extract at doses of 5.0 and 10.0 mg/kg exerted no significant effect on AChE activity in the brain.

Discussion

AD is a neurodegenerative disorder associated with a decline in cognitive abilities (2,3). Nootropic agents like, piracetam and cholinesterase inhibitors like, Donepezil® are commonly used for improving memory, mood and behavior in AD (2). However, the resulting adverse effects of these drugs such as diarrhea, insomnia, nausea, bronchitis, loose stools, muscular cramps and other known side effects (2,3), has made their use limited and it is worthwhile to explore the utility of traditional medicines in the treatment of various cognitive disorders. In the early stages of this neurodegenerative process it is more pronounced in cholinergic-type brain centres. One of the most notable of these is the amount of attention recently being paid to the enzyme AChE, which increases the bioavailability of the neurotransmitter in the cholinergic synapses by preventing the hydrolysis of acetylcholine (9). Herbal medicines can be used in the treatment of AD (13).

We investigated the effects of repeated polyprenols extract treatment during 14 days on cognitive abilities in male rats with scopolamine-induced amnesia. For this purpose, the passive avoidance test and Morris water maze were used in the study. Our results showed that in rats treated with scopolamine, there were marked memory impairments as assessed by passive avoidance test and Morris water maze. Our results also demonstrated that in rats with scopolamine-induced amnesia, there were an increase of AChE activity. We found that polyprenols extract treatment at dose of 1.0 mg/kg per se significantly ameliorated and the impaired cognitive performance induced by scopolamine injection in the rats. On the other hand, polyprenols extract treatment at dose of 1.0 mg/kg significantly increased locomotor activity, rearing and grooming events and so significantly reversed the behavioral impairments in the rats with scopolamine-induced amnesia in the OFT. However, the results

from other rats given with polyprenols extract treatment at doses of 5.0 and 10.0 mg/kg indicate that polyprenols extract treatment at dose of 1.0 mg/kg affects memory-related processes rather than motor function. The OFT results in this study suggested that polyprenols extract treatment at dose of 1.0 mg/kg to the rats with scopolamine-induced amnesia completely restored the impaired memory abilities. Biochemical data showed that polyprenols extract treatment at dose of 1.0 mg/kg significantly decreased and completely restored AChE activity in the brain of the rats with scopolamine-induced amnesia. Interestingly, administration of polyprenols extract at doses of 5.0 and 10.0 mg/kg failed to modify AChE activity in the brain of the rats with scopolamine-induced amnesia. It could be suggested that polyprenols extract modulates AChE activity and normalizes cholinergic neurotransmission in the brain of the rats with scopolamine-induced amnesia. In this connection, our future investigations will aim to clarify how polyprenols extract treatment alters functional activity of cholinergic system in the brain.

Taken together, it can be proposed that the positive effect of chronic polyprenols extract treatment on cognitive-related brain function after impairment induced by scopolamine is connected with its mutual and complex action on the cholinergic system and/or on oxidative stress. Furthermore, this is the first study to show beneficial effect of chronic polyprenols extract administration on memory impairments induced by scopolamine.

Conclusion

In conclusion, the results of the present study suggest that chronic polyprenols extract treatment results in cognitive-improving effects of the rats in the passive avoidance test and Morris water maze in an animal model of scopolamine-induced amnesia. In general, the results of this study indicate that polyprenols extract has a pronounced memory-enhancing efficacy in the management of the experimental model of amnesia induced by scopolamine. It also has a profound beneficial effect on cognitive impairments of the rats with scopolamine-induced amnesia, and so may well prove to be a novel, natural basic or adjuvant treatment. We suggest that polyprenols extract may be used as an adjuvant therapy along with other drugs against AD to prevent progressive trends of AD. Combined treatment with polyprenols extract and different drugs for AD treatment (applied in the clinic) may be an alternative to the treatment of amnestic-resistant AD-patients in the future. However, longitudinal clinical trials are needed to prove this hypothesis. We believe these results deserve further investigation.

Conflict of interest

The authors declare that they have no competing interests.

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ВВЕДЕНИЕ ЭКСТРАКТА ПОЛИПРЕНОЛОВ КОРРЕКТИРУЕТ ВЫЗВАННЫЕ ВВЕДЕНИЕМ СКОПОЛАМИНА РАССТРОЙСТВА ПРОСТРАНСТВЕННОГО И НЕПРОСТРАНСТВЕННОГО ОБУЧЕНИЯ У КРЫС

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Настоящее исследование было разработано с целью изучения влияния хронического введения экстракта полипренолов в капсулах (1.0, 5.0 или 10.0 мг/кг, перорально, 1 раз в день, 14 дней) на процессы обучения и памяти в условиях экспериментальной модели амнезии, обусловленной введением скополамина (1.0 мг/кг, подкожно, 14 дней). Тестирование процессов обучения и памяти проводили в тестах условная реакция пассивного избегания (УРПИ) и в водном лабиринте Морриса, двигательную активность и поведенческие реакции оценивали в тесте «открытое поле». Кроме того, с помощью иммуноферментного анализа проводилось определение активности ацетилхолинэстеразы в гомогетатах головного мозга крыс с экспериментальной моделью скополаминовой амнезии на фоне введения экстракта полипренолов в капсулах. Установлено, что введение экстракта полипренолов в капсулах в дозе 1.0 мг/кг, достоверно улучшало воспроизведение УРПИ и пространственное обучение в тесте Морриса у крыс с экспериментальной моделью скополаминовой амнезии, а также повышал двигательную активность и представленность груминга. Биохимический анализ показал, что экстракт полипренолов в капсулах в дозе 1.0 мг/кг активность

фермента ацетилхолинэстеразы в головном мозге крыс с экспериментальной моделью скополаминовой амнезии.

Таким образом, результаты настоящего исследования свидетельствуют о том, что хроническое введение экстракта полипренолов в капсулах корректирует амнестические функции и устраняет амнезию, вызванную введением скополамина, в тестах на пространственное и непространственное обучение.

Ключевые слова: ацетилхолинэстераза, экстракты полипренолов, обучение, память, скополамин.