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The Central Effects of Saponin Components and Polysaccarides Fraction from Korean Red Ginseng

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Abstract□To investigate the significant indicators improving the undisturbed memory in animal behavior, we employed several behavioral methods (learning, relearning in radial maze, and active avoidance) with ginseng components. Results showed that the repeated intranasal administration of Rb_1 and total saponins from Korean red ginseng induced direct effects on the brain mechanisms in rats, and improved the spatial memory during the learning, relearning and retention in the 12-arm radial maze test. The intranasal treatment of the total saponins also effectively improved the disturbed memory (amnesia) by pentylentetrazole, and simultaneously protected the brain by decreasing the severity of motor epileptic seizures. The intraperitonial administration of polysaccharide fraction of Korean red ginseng could improve avoidance behavior (amount of the total ecapes) in the active-avoidance test. In addition, local changes of the temperature and resistance of skin observed after Rb_1 administration were suggested to reflect some action of sympathetic nerve.

Key words□Memory, intranasal administration, pentylenetetrazole, Korea red ginseng.

Introduction

Korean red ginseng can be used for treatment and prevention of many diseases. The history of traditional Oriental medicine showed many examples of successful ginseng applications, especially for mental illnesses, psychosomatic diseases related to the ages, i.e. during "gerontological fading". Should this experience be explained on the bases of modern molecular performances ?

More successful study in recent years has been done on saponins and individual compounds of the Korean red ginseng (Rb_1, Rg_1, Rc etc.) to the molecular processes into the brain. Their effects were also investigated on the central cholinergic transmitter systems.[1]

In the comparison of the other biological active substances, ginsenosides showed the nootropic pharmacological spectrum of actions.[2,3] The important things among these nootropic properties are: ① acceleration of the memory consolidation, ② antihypoxic effect, ③ increasing the resistance of the central nervous system to injuring agents: electric shock, trauma, intoxications.[4]

Unfortunately, the neurochemical mechanisms of nootrops are not yet clear, but it is our general feeling that the research of individual ginsenosides of Korean red ginseng may provide a helpful understanding in the "nootropic phenomenon" of the brain.

The nootropic effects of ginseng have been studied in detail by Petkov *et al.*[2] It has been shown that ginseng shortened the latencies of the positively conditioned responses and produced a differentiation to the positively or negatively conditioned stimuli, together with the facilitated performances in human and animal activities. In many cases, however, the ginseng induced changes which seemed as if the brain activity was a more complex and even opposite character.[5] Attention was substantia-

lly increased during the period of behavioral test in rats treated with ginseng fraction.[6, 17] Therefore, it might be possible to improve undisturbed memory in both humans and experimental animals.

Recently, we demonstrated the improving effects of triol saponins on the spatial memory of learned rats in radial maze.[7]

In this study we employed behavioral methods (learning, relearning in radial maze, and active avoidance) and physiological tests (measurement of temperature and electroresistance of skin, rota-rod and tail-flick methods). Repeated administration was preferred to use rather than intermittent injections considering the therapeutic effects of ginseng (like other nootrophs) during the consecutive treatment. The main aim of our investigation was to develop the significant indicators improving the undisturbed memory in animal behavior models. New effective route of administration[8] of ginseng (intranasal) was also achieved in view of the final influence of Rb_1 and saponins on the spatial memory, which is dependent on the cholinergic system of limbic system of brain.

Materials and Methods

1. Animals

Male Mongrel rats (200~250 g b.w.) of Wistar lines were used. The room was illuminated from 07 : 00 to 19 : 00.

2. Drugs

Total saponons (TS), Rb_1 and polysaccharides fraction (PS) were prepared from Korea Ginseng & Tobacco Research Institute.[20, 21] Intraperitoneal (Rb_1-0.5 mg, 2 mg, 10 mg/rat in 0.1 m*l* saline; polysaccharide-0.1 mg, 1 mg, 5 mg/rat) and intranasal (saponins and Rb_1-20 μg in 20 μ*l* saline) pathways of administration were used. Pentylenetetrazole (PTZ) (Research Biochemicals International, USA) was injected i.p. in a dose of 50 mg/kg.

3. Apparatus and Procedures

The symmetrical 12-arm radial maze was constructed from clear plastic according to Olton[18] and Bures.[9] The arms were constructed from black plastic tubes with doors opened into the arm at the begining and - out into the end. Illumination was provided by upper light and by light from two windows. Surrounding the maze was a rich variety of extramaze stimuli, including tables, experimentalists and computers, posters on the walls. All markers did not change up to the end of experimental work.

Prior to the present experiment the rats were adaptated for 6 days in the maze with opened doors into the arms and with the positive alimentary reinforcement (peices of cheese). Every day only one session of training was done. The passages into the arms, the errors (working memory) of repeatedly visiting into the arms and strategy of behavior were registered automatically by computers PDP-11/30 (Q-bus LSI 11) after TV controller.[10] Before training the rats did not receive any food at least 8 hrs.

Rats were considered to have passed when they visited all 12 arms during constant time (3 min). Training was carried out from 14 : 00 at the same time every day. In the case of relearning only 6 arms (from the 1st to the 6th arm) were reinforced among the 12 arms.

The apparatus of "Columbus Instruments Co., (USA)" were used for active avoidance test (shuttle-box). Details of experimental approach and common procedure for active avoidance training have been provided in the reference already cited.[2] The conditioned signals (sound) were combined with electric shock (alternative current, 5 V., along the flow grid) reinforcement.

The rats were tested along with hardware (rigid) program; duration of the signal (3 sec.)-delay (4 sec.)-electroshock (4 sec.)-intersignal (intertrial) interval (4 sec.). In this procedure the conditional reflex can cross with the unconditional reflex. Each rat was trained for 5 days before and after the administration of the polysaccharides for 6 days. In the training session 10 trials were carried out everyday.

For tail-flick test and rota rod test standard apparatus "Columbus Instrument Int. Co." were used.

The skin electroresistance was measured by a special system "PROGNOS-mini" (Berdsk, Russia).[11] The current 12 μA, duration of impulse 250 msec nominal voltage 6~15 V were used. The electrode

with 3.5 mm diameter was pinned to skin by a special spring. Standard of pressing has been reliably secured by design. The symmetric points of rat's forelimbs skin were measured. The temperature of skin was measured by a special electrothermistor.

Differences between experimental and control rats were statistically evaluated by means of Student's test and Wilkoxon test.

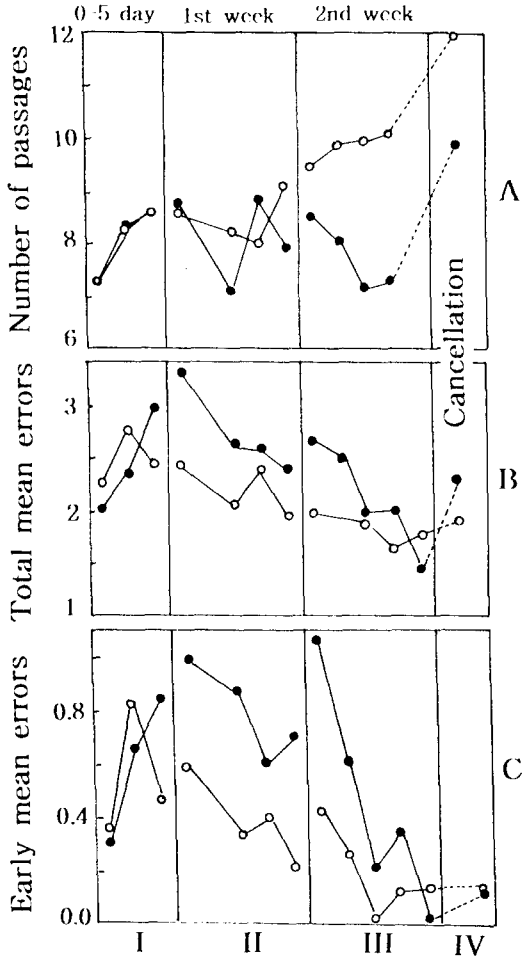

Fig. 1. Effect of ginseng saponin fraction (TS) on the training of rats in the 12-arm radial maze during daily intranasal application. The dosage of saponin fraction was 20 μg. A: Amount of visited channels in one test per rat. B: Working memory; Total amount of errors. C: Reference memory; The early errors during the visit from the 1st to 6th channel. I: Before administration for 5 days. II: The 1st week, and III: The 2nd week administration of TS. IV: One day after cancellation of administration of TS. Open circle represents control, water administration and black circle represents groups administered saponin fractions (TS). Each group of animals used 10~11 rats.

Results

1. The improveing effects of Rb_1 and total saponins on the spatial memory

The learning into radial maze : We confirmed the earlier observation[13] that Rb_1 and saponins (TS) showed activity at concentration less than 1 mg/rat after i.p. administration. In recent investigation we also examined the effects of total saponins by using another pathway of application. Daily intranasal ad-

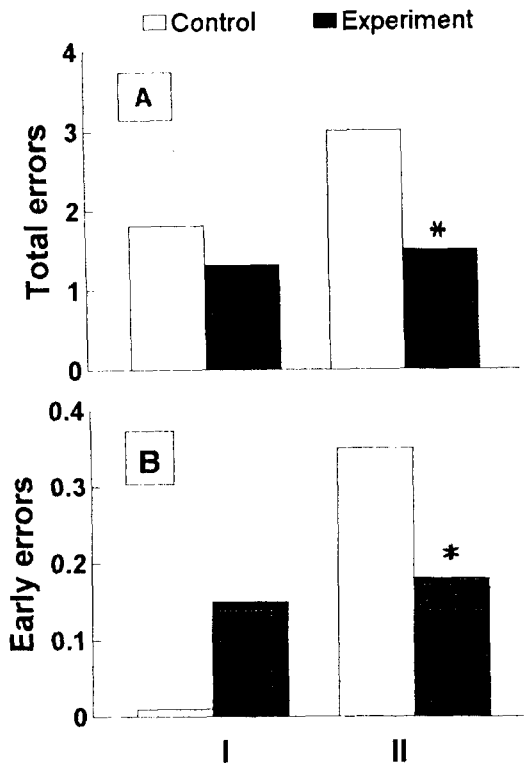

Fig. 2. Maintenance of memory after one month of cancelation of saponin (TS) administration. Comparison of the amount of total (A) and early (B) errors. I: Sixteen days of training. II: The results of test on 55 days of experiments, one month after cancellation.

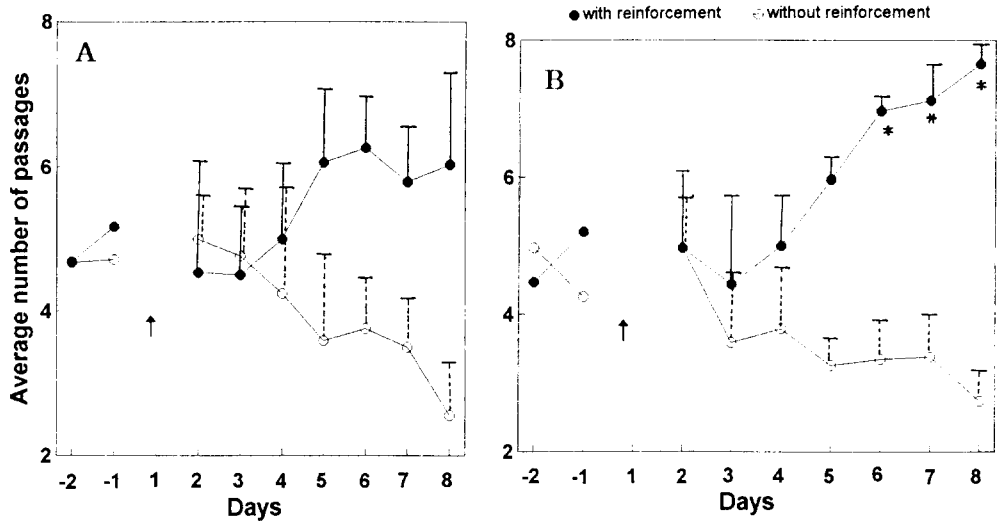

Fig. 3. Effect of ginsenoside Rb_1 on the rats retrained in the 12-arm radial maze with the 6/6 symmetrical channels with/without reinforcement. A: Control, B: Experimental group. Before the arrows all 12 arms were put a piece of cheese (reinforcement), and after arrows- only 6 (from 1st to 6th) channels were reinforced. Closed circles represent passage of reinforcement channels. Open circles- not reinforcement. *The last three days of relearning were significantly different in only Rb_1 administratin ($p<0.01$, Wilkoxon test) (2 mg/rat).

ministration in a dose of 20 μg/rat showed that, after 1 week treatment, the behavior of rats into radial maze was different between control and saponin treated groups (Fig. 1). In spite of the decreasing the passage into the maze in the experimental rats they have completely learned (Fig. 1 cancellation) with lower level of errors (Fig. 1, total mean errors). The retention of memory was examined after one month rest. The result of 16th days of learning into radial maze (Fig. 2-I) and one month after saponin cancellation was compared in Fig. 2-II. Significant difference between treated and control groups of rats was demonstrated in amount of total errors as well as in the amount of the early errors, when rats passed the first 6 arms. The present experiment showed that the improving influence of saponin remained until one month after learning.

2. The relearning of rats in 12-arm radial maze with 6 reinforcement arms

The sifnificant improving effect of ginsenosides was demonstrated during 7 days relearning of rats into radial maze (Fig. 3). According to paradigm of this experiment the amount of passage into reinforecement channels should have been increased, but unreinforcement channels decreased to zero. The rats treated with Rb_1 visited into reinforcement channels more fast, that is, data were manifested by improving the memory processes. The differences between passages of reinforcement and nonreinforcement channels were significant in the experimental group only as compared with control group.

3. The protective action of total saponins on cognitive functions and severity of seizures during PTZ-induced amnesia

In order to elucidate the improving properties of ginseng on disturbing memory, the model of PTZ-amnesia was investigated. PTZ in a dose of 50 mg/kg b.w. was induced motor seizures and also was accompanied by amnesia effect. In this study, the various aspects of total saponin treatment were investigated. At first we administered PTZ intranasally to the rats which have been received total saponin during one month (Fig. 4-I). Significant difference between treated group with saponin (A) and saline groups (B) was demonstrated. There was no significant difference after intraperitonial administration of saponins, but repeated intranasal adminis-

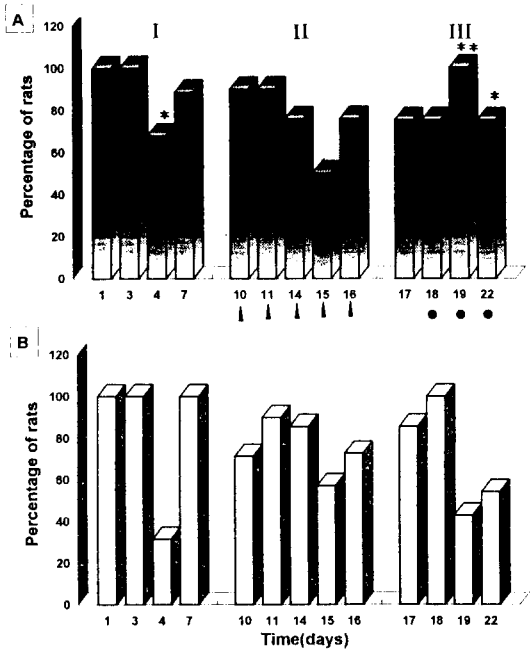

Fig. 4. Protective effect of ginseng saponin fraction (TS) on the cognitive functions in rats. Percentage of rats was demonstrated for the spatial memory of reference in 12-arm radial maze test. Fig.(A) is experimental (n=10), and Fig(B) is control (n=10) group. The 4th, 15th and 19 th day were induced PTZ (pentylenetetrazole) amnesia by injecting the PTZ intraperitonially in dose of 50 mg/kg b.w. * and ** represent significant differences between control and experimental groups, *$p<0.05$, **$p<0.01$. The experiments were divided into three parts (I, II, III). The rats received saponin fractions (TS) via intranasal (i.n.) administration during one month. The 1st PTZ amnesia was induced at 4th day after one month i.n. administration without additional saponin treatment (I), the 2nd PTZ amnesia was induced at 15th day (II) with additional i.p. treatment of saponin in a dose of 10 mg/rat (arrows indicate each treatment of saponin), and the 3rd PTZ amnesia (III) was induced at 19th day of experiment after i.i. administration of saponins in a dose of 20 μg (●).

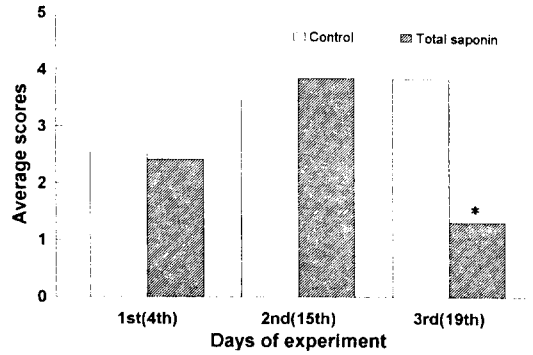

Fig. 5. Severity of pentylentetrazole-induced seizures in rats which have cognitive functions presented in Fig. 4. PTZs were administered 3 times (the 4th, 15th, and 19th day) during the experiment as discribed in Fig. 4. *The significant difference between 1st and 2nd seizures and between control and experimental group in 3rd severity were accepted as $p<0.01$ and $p<0.05$, respectively, in Student's t-test.

tration of saponins (18~22 days, Fig. 4) was very effective. The normalization of the cognitive function was compared with severity of seizures (Fig. 5) and latency of epileptical fits in rats (Fig. 6).

The first PTZ administration induced equal severity with the same latency (Fig. 5, 6-4th day). The result of the second PTZ administration showed significantly more strong severity both in experimental and control group (Fig. 5, 15th day, the clonic-tonic motor seizures-4 scores by Maresh[19]) than the 4th day. It is reasoned that cognitive function was disturbed equaly in both experimental and control rats. In the 3rd PTZ administration the protective effects of saponins was observed as to cognitive functions (Fig. 4, III), as well as severity of motor seizures (Fig. 5, 19th day). The improvement of the cognitive functions by the treatment of saponin after PTZ-induced amnesia had a correlationship with the positive effect of saponin on the epileptical seizures, however, it was not accounted as a continuous phenominon. The significant difference between 1st and 2nd latency of seizures was $p<0.05$ in Wilcoxon test but, there was no significance statistically between control and experimental group in Fig. 6.

4. The influence of polysaccharides fraction (PS) from Korean red ginseng on the active-avoidance behavior in rats

The character of avoidance behavior in the rats chronically treated with PS : One control and three experimental groups of rats learned shuttle-box

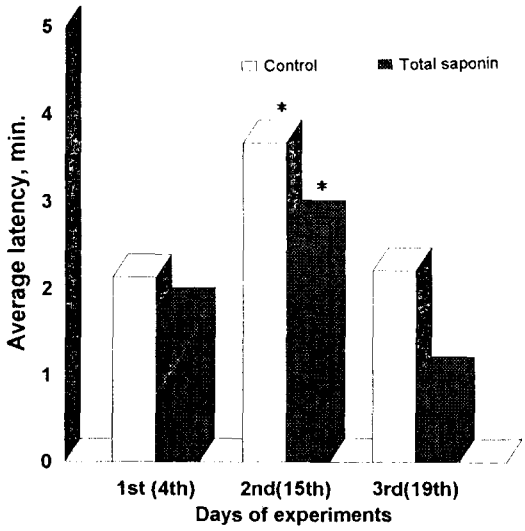

Fig. 6. Latency time of pentylentetrazole-induced seizures in rats which have cognitive functions presented in Fig. 4 and 5. PTZ were administered i.p. 3 times.

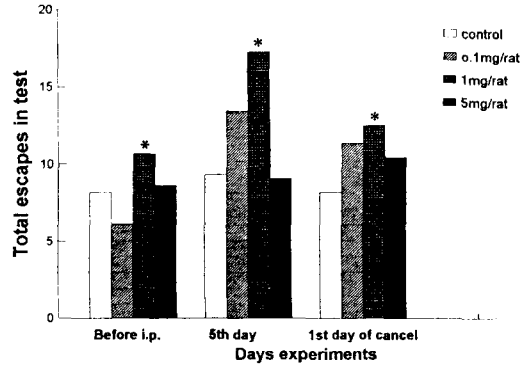

Fig. 7. The effects of polysaccharides on the learned rats in the active-avoidance test. Average data of total escapes presented before (I), on 5th day administration of polysaccharides (II) and 1st day after cancellation (III). Control group: n=15. Experimental groups: 0.1 mg, n=15; 1 mg, n=14; 5 mg, n=12. *p<0.05 (Wilkoxon test).

(one-way) how to behave for 5 days. The polysaccharides (PS) were daily administered 30 min before test i.p. during 6 consecutive days. All groups of rats demonstrated the equal average time of avoidance (1.3~1.5 sec.) before treatment with PS. As shown in Fig. 7 the significant changes of total

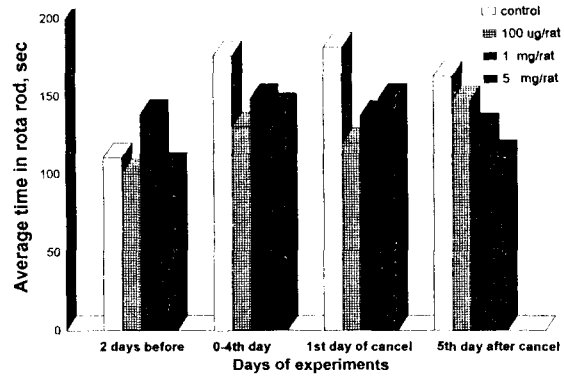

Fig. 8. The effect of polysaccharides administration on the time of keeping in rota rod test. *p<0.05 for the control value (Student's test).

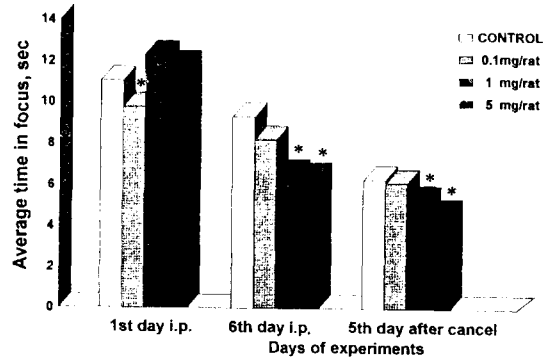

Fig. 9. The effect of hyperalgesia in tail-flick test in rats after 5 days treatment by polysaccharides i.p. *p<0.05 for the control value (Student's test).

escapes were observed in the experimental group treated chronically with PS in a dose of 1 mg/rat. These data confirm that ginseng compounds can influence on the quantitative character of behavior. The quality of escape behavior was defined as compared with the saline treated group by the amount of total escape after conditional signal.

5. The changes of motor and sensor systems in rats after administration of polysaccharides fraction

The effects of PS on functional state of central nervous system were examined by using rota rod test (Fig. 8) and tail-flick test (Fig. 9). No significant changes on the 1st day i.p. ihave been observed after PS treatment with dose of 1 mg and 5 mg/rat.

Table 1. The effects of ginsenoside Rb_1 (0.5 mg/rat i.p.) on the electrocutaneous resistance and temperature of dosal paw skin in rats (average, right forelimb). Experimental group n=10, Control group n=8

	2nd day stress	1st day	1st day before Rb_1 after Rb_1	2nd day before Rb_1 after Rb_1	3nd day before Rb_1 after Rb_1	4th day cancel	5th day
Electrocutaneous Resistance (kOm)							
Exp.	2.79± 0.39	2.27± 0.24	3.09± 0.45 2.83± 0.40	2.18± 0.24 2.83± 0.11	2.10± 0.22 1.66± 0.20	1.77± 0.12	3.08± 0.33
Contr.	1.94± 0.20	1.82± 0.20	1.61± 0.16 1.48± 0.10	2.24± 0.17 1.68± 0.60	2.65± 0.30 2.28± 0.40	2.70± 0.30	2.23± 0.3
Temperature (℃)							
Exp.	32.0 ± 0.3	30.2 ± 0.2	30.4 ± 0.2 31.0 ± 0.3	30.4 ± 0.2 31.0 ± 0.1	30.5 ± 0.1 31.0 ± 0.2	31.6 ± 0.1	30.7 ± 0.3
Contr.	31.2 ± 0.2	30.1 ± 0.4	31.5 ± 0.2 31.2 ± 0.4	30.7 ± 0.2 31.1 ± 0.3	29.8 ± 0.2 29.7 ± 0.7	30.8 ± 0.2	30.4 ± 0.2

Table 2. The effects of ginsenoside Rb_1 (0.5 mg/rat i.p.) on the electrocutaneous resistance and temperature of dosal paw skin in rats (average, left forelimb), (n=8~10)

	2nd day stress	1st day	1st day before Rb_1 after Rb_1	2nd day before Rb_1 after Rb_1	3nd day before Rb_1 after Rb_1	4th day cancel	5th day
Electrocutaneous Resistance (kOm)							
Exp.	2.57± 0.40	1.83± 0.29	2.04± 0.21 2.01± 0.25	1.53± 0.12 1.54± 0.60	1.71± 0.21 1.75± 0.29	1.54± 0.12	2.22± 0.22
Contr.	1.94± 0.20	1.59± 0.24	1.59± 0.16 1.41± 0.01	1.70± 0.21 1.43± 0.10	1.72± 0.13 1.63± 0.24	2.04± 0.28	1.42± 0.68
Temperature (℃)							
Exp.	32.3 ± 0.2	30.2 ± 0.2	30.7 ± 0.2 31.6 ± 0.2	30.9 ± 0.1 31.4 ± 0.2	31.2 ± 0.1 31.8 ± 0.2	32.2 ± 0.1	31.3 ± 0.1
Contr.	31.6 ± 0.2	30.6 ± 0.2	31.8 ± 0.2 31.8 ± 0.3	31.0 ± 0.1 31.0 ± 0.3	30.0 ± 0.1 29.7 ± 0.3	30.0 ± 0.1	30.7 ± 0.2

Evidently the polisaccharides did not influence on the motor coordination, subcortical and spinal mechanisms of coordination in these doses. As to sensory mechanism the treatment with PS induced the hyperalgesis in tail-flick test (Fig. 9). On the 6th day after i.p. administration of PS the significant decrease of average time (n=15 rats in each group) was observed. The effect was dose dependent. This increasing sensitivity to pain continued to some extent until 5 days after cancellation of administration.

The hyperalgesia observed in rats in our experiments may play some key roles in determining the velocity of learning in passive avoidance test which depends upon the painful reinforcement.

6. Effects of ginsenoside Rb_1 on the electroresistance and temperature of skin in rats

Rb_1 indirectly changes the electrocutaneous resistance and the temperature of front paws' skin after systemic administration (i.p. in this experiment). The results of measurement are presented in Table 1 and 2. The symmetric points of forelimbs in skin simultaneously reflected the decreasing resistance after Rb_1 administration as compared with the data

before and 30 min after administrations. Common decrease of the resistance was observed after 3 days of treatment with Rb_1. The significance of difference was analysed by the Wilkoxon's test. In any cases between control and experimental groups, between days: before, during and after Rb_1 administration, between left and right forelimb's skin-significant changes ($p<0.05$) were obtained. The differences of resistance on the two symmetric points of skin in the left and right forelimbs were demonstrated as a functional asymmetry of sympathetic descending influences after ginsenoside Rb_1 administration.

The local temperature of skin in rats treated with Rb_1 was significantly increased in comparison with the saline injected group.

Discussion

The results of this study have made a clear point that the treatment of Rb_1 or total saponins improved undisturbed memory and also protected the memory consolidation and the retention. It is needed to agree with Petkov's note[5] "effect was somewhat different depending on the method".[5] Our study was the first trial on the influences of the spatial memory, using paradigm of symmetrical radial maze. The radial maze was introduced as a tool for the study of spatial memory. In our experiments the repeated administrations of Rb_1 as well as the total saponins were both effective. The correct choices of criteria gave a help to demonstrate the further data on what is more effective on the "reference memory" or "working memory" among Rb_1 and saponins.

Our data are in accordance with the positive influences of ginseng compounds and Rb_1 on the cholinergic system of brain. The spatial memory disturbed by antagonists of cholinergic system, should be determined whether its normalized action on the acetylcholine uptake might be improved by the ginseng treatment or not. Behavioral procedures have to be confirmed whether ginseng compounds will improved the cognitive funcations of animals or not.

A hypothesis could be established by manifesting the results especially for relearning processes determined the pathway of administration. We used intranasal applications which were developed by Ashmarin and coauthors[8] on Rb_1 and saponins that was effective directly on brain structures. Our earlier studies of neuropeptides actions (TRH, MIF1, AVP, kassinin) on the brain function with the isotops distributed in the brain, CSF and blood showed that intranasal administration of small and ultra-small doses was so effective.[12]

The other paradigm of memory test used in our study was avoidance behavior. In this case our results also confirmed the previous data[2,5,6,13] with improving effect of ginseng but not with regard to the polysaccharides. In this study the improvement of the quality of behavior was demonstrated: the total escapes were increased after repeatedly i.p. administration of polysaccharides. This paradigm of experiment has been well studied by many authors who had used both passive-avoidance and active-avoidance tests. Jaenicke and Kim[6] noted that positive effects of ginseng on the cognitive performance did not connected with arousal, because the rats did not change behavior in the open field. Recently Ma *et al.*[13] showed that saponins in stem-leaves improved avoidance behavior and shortened the latency of normal avoidance and prolonged avoidance by scopolamine.

It is necessory to note that the avoidance behavior induced the painful reinforcements (electric-shock by paws). The neurochemical mechanisms of this kind of reinforcement (motivation) were very different from positive alimentary reinforcements in radial maze. Avoidance behavior is connected with pain threshold and the sensitivity of animals, consequently, determined by peripheral injection of neuropeptide tachikininergic system: nerve endings and cells are containing SP, neurokinin A and CGRP.

We obtained new and the first data about effects of Rb_1 on the electroresistance of skin, that can be also determined the tachikinins systems of afferent nerve endings in the skin. The effects of ginseng compounds on tachikinins would be perspective problems for research and clinical applications. In our study, for the first time, we measured the

skin resistance after systemic injection of Rb_1. The changes of skin resistance may reflect the normalization of microcirculation of blood and electrolytic balance in the skin.[14]

The important question is how the motor system of brain has influenced the processes of learning and memory in the instrument and moving tests, if the ginseng compounds influence on the motor functions. Lee and coauthors[3] demonstrated that the total saponins have a little effect on the locomotor activity, as in more higher doses (50 mg/kg). Rb_1 and total saponins showed very weak actions on the apomorphine induced stereotypy and consequently, other compounds of ginseng (PT, Rg_1) acted on the central dopaminergic system.[3,15] Our results suggest that the investigated mechanisms of memory improvement can be participated in the cholinergic system of the brain.

As to the effects of ginseng on the experimental dementia, Kumagai[16] showed that crude saponins can prevent hippocampal ischemia of neurons and also prevent significantly the impairment of memory retention. We also agree that the target for ginseng actions in the brain was hippocampus which is believed to be decisive in the spatial memory and "the congnitive map of brain". In this study we, for the first time, demonstrated the preventive effects of the total saponins not only for pentylenetetrazole amnesia but for the motor seizures which were usually induced by this epileptogene. The neurochemical mechanisms of these phenomenon is not yet clear. The very important problems for clinics of epilepsy needs to be investigated in detail in the future.

요 약

동물 행동모델을 이용한 인삼성분들의 정상기억력 증진의 지표들을 찾기위해 방사미로에서의 학습능력, 능동회피반응 등을 조사하였다. 진세노사이드 Rb_1 및 고려홍삼 총사포닌을 반복해서 점막투여한 결과, 12-arm 방사미로에서의 학습, 재학습 동안의 기억 등에 관여하는 과정에 이들 성분들이 직접 영향을 주는 것으로 나타났다. 랫드의 코점막을 통해 홍삼 총사포닌을 투여하면 Pentylene-tetrazole에 의해 유발되는 건망증(disturbed memory)이 개선되었으며 동시에 운동성 간질발작에 의해 저하된 뇌기능을 보호하였다. 고려홍삼 다당체분획의 복강투여는 능동회피반응 시험에서의 회피행동을 개선시킬 수 있으며, 그 밖에 Rb_1 투여 후 관찰되는 피부온도 및 저항성의 국소적인 변화는 교감신경에 영향을 미치는 것으로 추정된다.

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