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Original Research

Effect of astragaloside IV on cognitive dysfunction in rats with cerebrally infarcted via TGF-β / Smad signaling pathway

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Abstract: Cerebral infarction is an acute cerebrovascular disease caused by abnormal blood circulation in the brain. In the present study, we investigate the effect of astragaloside IV on cognitive dysfunction in cerebrally infarcted rats via transforming growth factor-β (TGF-β) / Smad signaling pathway. For this purpose, 45 rats were divided into three groups including astragaloside, model, and control. 30 of 45 healthy adult male SD rats were randomly selected to establish an acute cerebral infarction model. 15 modeled rats were enrolled as a model and astragaloside group, and another 15 rats as a blank control group. The rats in the astragaloside group were fed with astragaloside IV according to 1.08 g/kg body weight, and those in the blank group and model group were given matching normal saline. The levels of TGF-β, Smad1, Smad3 and Smad7 of TGF-β/Smad signaling transduction pathway at T0 (week 0), T1 (week 3) and T2 (week 6) were determined by enzyme-linked immunosorbent assay (ELISA). The modified neurological severity score (mNSS) was used to evaluate the improvement of cognitive dysfunction in rats. The mNSS of rats with cerebral infarction in the astragaloside group was lower than that in the control group and model group ($P< 0.05$). While the levels of TGF-β, Smad1, Smad3 and Smad7 in the astragaloside group were higher than those in the control group and model group ($P< 0.05$). Astragaloside IV plays an important role in improving cognitive dysfunction in rats with cerebral infarction while affecting the levels of TGF-β, Smad1, Smad3 and Smad7 and activating TGF-β / Smad signaling pathway.

Key words: Astragaloside IV; TGF-β / Smad signaling pathway; Cerebral infarction rats; Cognitive dysfunction.

Introduction

Cerebral infarction, as a threat to the health and an important cause of mortality, is an acute cerebrovascular disease caused by disorders in the cerebral blood circulation process (1, 2), with high morbidity and mortality. Moreover, with the influences of the social environment and bad living habits, its incidence and mortality rate are still increasing year by year (3, 4). Moreover, as one of the three diseases with the highest mortality in the world, cerebral infarction poses a great threat to people's life and health (5, 6). Cerebral infarction is an area of necrotic tissue in the brain that spreads to the brain through the blocking or narrowing of blood vessels and oxygen. Limited oxygen can cause ischemic stroke due to limited blood flow. If blood flow is not restored within a relatively short period of time, it can lead to infarction. The obstruction may be caused by thrombosis of one or more arteries, embolism, or atherosclerotic stenosis which arteries have problems and determine which areas of the brain are affected (infarction). These infarctions can cause different symptoms and consequences. About one-third will be fatal (1-3).

Cognitive dysfunction is a direct clinical symptom leading to high morbidity and poor prognosis in patients with cerebral infarction (7).

The involvement of transforming growth factor-β (TGF-β) / Smad signaling transduction pathway in the pathological process of brain tissue injury can severely impair patients' cognitive function (8-10). Astragaloside IV, as a saponin monomeric compound, is an active ingredient extracted from Astragalus membranaceus (11, 12). Related reports have shown that it effects on inhibiting inflammatory cytokines (13). Therefore, this study explored the effect of astragaloside IV on cognitive dysfunction in rats with cerebral infarction via TGF-β / Smad signaling pathway in order to provide clinical references for improving cognitive function in cerebral infarction.

Materials and Methods

Subgrouping and administration

Materials: 45 healthy adult male SD rats were obtained from Shanghai Slac Laboratory Animal Co., Ltd., and 30 of them were randomly selected to establish an acute cerebral infarction model. 15 modeled rats were enrolled as a control group and astragaloside group, and another 15 as a blank control group. The rats in the astragaloside group were fed with astragaloside IV according to 1.08 g/kg body weight, and those in the blank group and model group were given matching normal saline. Metabolic data were collected every 3 weeks and the rats were sacrificed 6 weeks after administration. All rats received a weekly intramuscular injection of penicillin sodium (Shanghai Baoman Biotechnology

Table 1. Comparison of general data among the three studied groups.

	Astragaloside	Model	Control	*F*	*P*
Weight after modeling (g)	220.81±10.61	222.40±10.32	221.64±10.51	0.086	0.917
Weight before modeling (g)	168.46±7.32	168.53±6.89	169.21±6.05	0.056	0.946
Length (cm)	18.79±1.24	19.11±1.12	18.96±1.03	0.299	0.743
Age (week)	8.20±0.41	8.30±0.24	8.22±0.37	0.348	0.709
Glucose (mmol/L)	82.51±11.19	81.44±12.16	82.24±11.65	0.034	0.967

Co., Ltd., art. no: K0031).

Establishment of acute cerebral infarction model

Middle cerebral artery occlusion models of acute cerebral infarction were established with modified Longa' suture-occluded method on the right side of rats (14). The Zea Longa 5-point scoring method was used to evaluate (15) the establishment of models. When the rats walk without obstacles, the signs of body tilting to the hemiplegia side and turning circles indicate that the models of acute cerebral infarction were successfully established.

Main reagents and detection methods

Enzyme-linked immunosorbent assay (ELISA) test kit for TGF-β (Shanghai Guyan Biotechnology Co., Ltd.); ELISA test kit for Smad1 (Qingdao Jie Shi Kang Biotechnology Co., Ltd.); ELISA test kit for Smad3 (Qingdao Jie Shi Kang Biotechnology Co., Ltd.); ELISA test kit for Smad7 (Qingdao Jie Shi Kang Biotechnology Co., Ltd.); ELISA analyzer (Shanghai LNB Instrument Co., Ltd.).

ELISA was used to detect the levels of TGF-β, Smad1, Smad3 and Smad7. Blood was collected through vena caudalis puncture, centrifuged at 3500 r/min for 5 minutes, and then placed in a low-temperature refrigerator at 4 ℃ for use. The experimental steps were all carried out according to the instructions of the relevant ELISA test kits for TGF-β, Smad1, Smad3 and Smad7. Sample, standard and blank wells were set up respectively. 100 μL of sample diluent was added to the blank well, and 100 μL of sample or standard was added to the other wells. The plate was sealed with a closure plate membrane and then incubated at 37 ℃ for 30 min. Next, the membrane was removed carefully, the liquid being discard and the plate being dried. Afterward, washing liquid was added to each well, then discarded after 30-second standing. The wells were patted dry after the steps repeated 5 times. 50 μL of ELISA reagent was added to each well except the blank well. The wells were washed again after incubated at 37 ℃ for 30 min. The chromogenic agent was added to each well and well mixed. Then the development was carried out at 37 ℃ in dark for 15 min. 50 μl of termination solution was added to each well. The OD values were immediately detected at 450 nm wavelength using an ELISA analyzer, and the concentrations of TGFβ, Smad1, Smad3 and Smad7 were calculated respectively.

Outcome measures

The changes of TGF-β, Smad1, Smad3 and Smad7 levels in each group at T0 (week 0), T1 (week 3) and T2 (week 6) were recorded. The improvement of cognitive dysfunction of rats in each group at those time points was recorded with modified neurological severity scores (mNSS). The higher the score, the higher the degree of defect (16).

Statistical analysis

For statistical analysis, the SPSS 19.0 (Asia Analytics Formerly SPSS China) was used. The counting data were checked by the χ^2 test, and the measuring data were expressed by (x±S). The comparison among different time points in the group was conducted by repeated measurement analysis of variance (ANOVA), and expressed by F. LSD - T was used for the following pairwise comparison. When $P< 0.05$, the difference was statistically significant.

Results

Comparison of general data

There was no significant difference in general data among the three groups before and after modeling ($P > 0.05$) (Table 1).

Changes of TGF-β, Smad1, Smad3 and Smad7 levels in each group

Changes of TGF-β level in all groups

In astragaloside group, the expressions of TGF-β at T0, T1 and T2 were (0.53±0.06), (0.31±0.04) and (0.21±0.02) respectively, those in model group were (0.53±0.07), (0.60±0.07) and (0.65±0.06), and those in control group were (0.19±0.02), (0.19±0.02) and (0.19±0.01) respectively. TGF-β levels from T0 to T2 were gradually down-regulated in the astragaloside group, and the differences in TGF-β expression at different time points were statistically significant ($P< 0.05$). While those were gradually up-regulated in the model group, with statistically significant differences ($P< 0.05$). There was no significant difference in TGF-β expressions from T0 to T2 in the control group ($P> 0.05$). The expressions of TGF-β in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T1, but still higher than that in the control group, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T2, but still higher than that in the control group, with statistically significant differences ($P< 0.05$) (Figure 1).

ELISA results showed that the expressions of TGF-β in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences (*, $P< 0.05$). The expressions in the astragaloside group were lower than those in the model group at T1 and T2, but still higher than those

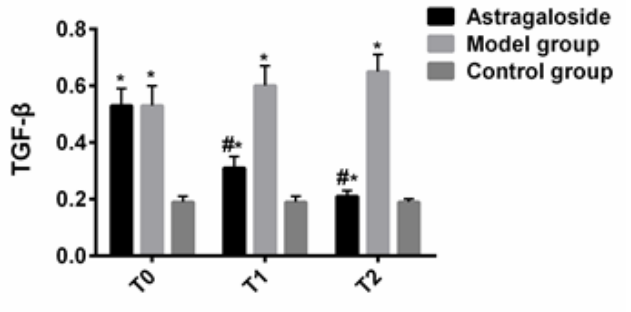

Figure 1. Changes of TGF-β level in all groups.

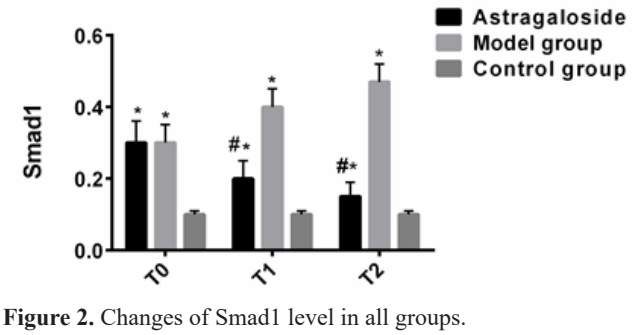

Figure 2. Changes of Smad1 level in all groups.

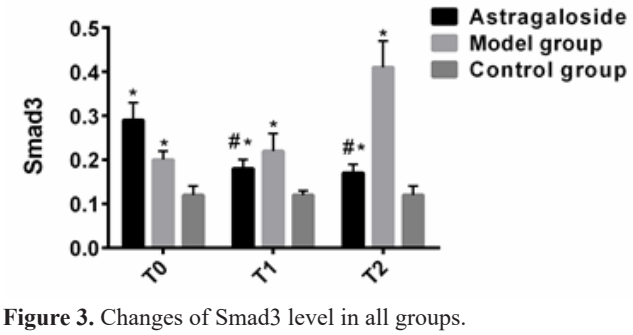

Figure 3. Changes of Smad3 level in all groups.

in the control group, with statistically significant differences (#, $P< 0.05$).

Changes in Smad1 level in each group

In astragaloside group, the expressions of Smad1 at T0, T1 and T2 were (0.30±0.06), (0.20±0.05) and (0.15±0.04), those in model group were (0.30±0.05), (0.40±0.05) and (0.47±0.05), while in control group were (0.1±0.01), (0.1±0.01), (0.1±0.01) respectively. Smad1 levels from T0 to T2 were gradually down-regulated in the astragaloside group, and the differences of Smad1 expression at different time points were statistically significant ($P< 0.05$). While those were gradually up-regulated in the model group, with statistically significant differences ($P< 0.05$). There was no significant difference in Smad1 expressions from T0 to T2 in the control group ($P> 0.05$). The expressions of Smad1 in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T1, but still higher than that in the control group, with statistically significant differences ($P < 0.05$). The expression in the astragaloside group was lower than that in the model group at T2, but still higher than that in the control group, with statistically significant differences ($P< 0.05$) (Figure 2).

ELISA results showed that the expressions of Smad1 in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences (*, $P< 0.05$). The expressions in the astragaloside group were lower than those in the model group at T1 and T2, but still higher than those in the control group, with statistically significant differences (#, $P< 0.05$).

Changes of Smad3 level in all groups

In astragaloside group, the expressions of Smad3 at T0, T1 and T2 were (0.29±0.04), (0.18±0.02) and (0.17±0.02), those in model group were (0.20±0.02), (0.22±0.04) and (0.41±0.06), and those in control group were (0.12±0.02), (0.12±0.01) and (0.12±0.02), respectively. The Smad3 levels from T0 to T2 were gradually down-regulated in the astragaloside group, and the differences of Smad3 expression at different time points were statistically significant ($P< 0.05$). While those were gradually up-regulated in the model group, with statistically significant differences ($P< 0.05$). There was no significant difference in Smad3 expressions from T0 to T2 in the control group ($P> 0.05$). The Smad3 expressions in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T1, but still higher than that in the control group, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T2, but still higher than that in the control group, with statistically significant differences ($P< 0.05$) (Figure 3).

ELISA results showed that the expressions of Smad3 in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences (*, $P< 0.05$). The expressions in the astragaloside group were lower than those in the model group at T1 and T2, but still higher than that in the control group, with statistically significant differences (#, $P< 0.05$).

Changes of Smad7 level in all groups

In astragaloside group, the expressions of Smad7 at T0, T1 and T2 were (0.43±0.03), (0.30±0.02) and (0.25±0.03), those in model group were (0.43±0.04), (0.52±0.02) and (0.59±0.02), and those in control group were (0.20±0.01), (0.20±0.02) and (0.20±0.01), respectively. The Smad7 levels from T0 to T2 were gradually down-regulated in the astragaloside group, and the differences in Smad7 expression at different time points were statistically significant ($P< 0.05$). While those were gradually up-regulated in the model group, with statistically significant differences ($P< 0.05$). There was no significant difference in Smad7 expression from T0 to T2 in the control group ($P> 0.05$). The Smad7 expressions in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group was lower than that in the model group at T1, but still higher than that in the control group, with statistically significant differences ($P< 0.05$). The expression in the astragaloside group

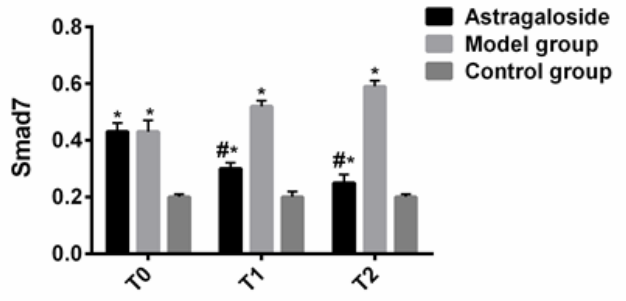

Figure 4. Changes of Smad7 level in all groups**.**

was lower than that in the model group at T2, but still higher than that in the control group, with statistically significant differences ($P< 0.05$) (Figure 4).

ELISA results showed that the expressions of Smad7 in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences (*, $P< 0.05$). The expressions in the astragaloside group were lower than those in the model group at T1 and T2, but still higher than those in the control group, with statistically significant differences (#, $P< 0.05$).

Improvement of cognitive dysfunction in each group

In astragaloside group, the mNSSs at T0, T1 and T2 were (10.12±0.76), (7.24±0.58) and (3.01±0.32), those in model group were (10.02±0.42), (12.30±0.52) and (14.27±0.62), while those in the control group were (0.00±0.00), (0.00±0.00) and (0.00±0.00), respectively. The mNSSs from T0 to T2 of rats were gradually down-regulated in the astragaloside group, and the differences of mNSS at different time points were significant ($P< 0.001$). While those were gradually up-regulated in the model group, with statistically significant differences ($P< 0.001$). There was no significant difference in mNSS from T0 to T2 in the control group ($P> 0.05$). The mNSSs in the astragaloside group and model group were higher than those in the control group at T0, with statistically significant differences ($P< 0.001$). The mNSS in astragaloside group was lower than that in the model group at T1, but still higher than that in the control group, with statistically significant differences ($P< 0.001$). The mNSS in astragaloside group was still lower than that in the model group at T2, but still higher than that in the control group, with statistically significant differences (P< 0.001). Details are shown in Table 2.

Discussion

In this experiment, we do not see a significant difference in general data in terms of body weight, length, age and glucose concentration of rats among the three groups before and after modeling. Therefore, the data interference factors in this test were reduced to some extent. As key genes in the TGF-β / Smad signaling pathway, the changes of TGF-β, Smad1, Smad3 and Smad7 levels in each group were observed. And it was found that, in the astragaloside group, the levels were gradually down-regulated from T0 to T2, and their expression levels were statistically significant at different time points. Whereas in the model group, the levels were gradually up-regulated from T0 to T2, and their expression levels were statistically significant at different time points. There was no significant difference in the expressions of TGF-β, Smad1, Smad3 and Smad7 in the control group from T0 to T2. The expressions of TGF-β, Smad1, Smad3 and Smad7 in the astragaloside group and model group were higher than those in the control group at T0, and the differences were statistically significant. While the expressions in the astragaloside group were lower than those in the model group at T1, but still higher than those in the control group, and the differences were statistically significant. The expressions in the astragaloside group were significantly lower than those in the model group at T2, but still higher than those in the control group. Relevant studies show that TGF-β participates in the proliferation and differentiation of cells and the pathological process of the cranial nerve system (17). Moreover, clinical indicators show that it also participates in the occurrence and development of cerebral infarction as an important reference index for its diagnosis (18). Meanwhile, Smads proteins have been proved to be involved in the occurrence and development of various brain tissue injury diseases (19-25). Therefore, it was speculated that the expression changes of TGF-β and Smads affected the pathological process of cerebral infarction via TGF-β/Smad signaling pathway in rats. Astragalus membranaceus is a traditional Chinese medicine widely used in many diseases, especially cardiomyopathy. Astragaloside IV is an extracted compound and one of the main active components of *Astragalus membranaceus* (26, 27). Previous experiments have proved that appropriate astragaloside IV can control inflammatory reaction by affecting TGF-β / Smad pathway signals, thus alleviating the patient's condition (28, 29). At present, some researches on cerebral infarction show that the inflam-

Table 2. Comparison of mNSS in three studied group.

Group	Astragaloside	Model	Control	*F*	*P*
T0	10.12±0.76*	10.02±0.42*	0.00±0.00	2017.00	<0.001
T1	7.24±0.58*#	12.30±0.52*	±0.00±0.00	3354.00	<0.001
T2	3.01±0.32*#	14.27±0.62*	0.00±0.00	5230.00	<0.001
F	566.300	244.900	0.000		
P	<0.001	<0.001	1.000		

Note: * indicates that mNSSs in this group are higher than those in the control group, with statistically significant differences ($P< 0.05$); # indicates that mNSSs in this group are lower than those in the model group, with statistically significant differences ($P< 0.05$).

matory response is closely related to the occurrence and development of cerebrovascular diseases (30, 31); Signal transduction in TGF-β / Smad signaling pathway aggravates inflammatory response of pathological tissues of patients (32). In combination with the statistical results in this study, it is believed that astragaloside IV can gradually reduce the levels of TGF-β, Smad1, Smad3 and Smad7 in rats with cerebral infarction. Next, mNSSs were recorded to observe the improvement of the cognitive dysfunction of rats. The results showed that the mNSSs from T0 to T2 were gradually down-regulated in the astragaloside group. While those were gradually up-regulated in the model group. There was no significant difference in mNSSs in the control group at various time points. The mNSSs in the astragaloside group and model group were higher than those in the control group at T0. The mNSS in the astragaloside group was lower than that in the model group at T1, but still higher than that in the control group. The mNSS in astragaloside group was lower than that in the model group at T2, but still significantly higher than that in the control group, and the differences were statistically significant. TGF-β and Smad have been proved to be involved in the occurrence and development of cerebral infarction (33). And a study has shown that the expression changes of key genes in the TGF-β / Smad signaling pathway of patients with cerebral infarction are important factors to accelerate cognitive dysfunction (34). Therefore, astragaloside IV plays an important role in improving cognitive dysfunction in rats with cerebral infarction while lowering the levels of TGF-β, Smad1, Smad3 and Smad7 (32-39).

There are still some deficiencies in this study. For example, only the levels of TGF-β, Smad1, Smad3 and Smad7 under the influence of astragaloside IV were studied in this study, and there was a lack of in-depth research and discussion on specific mechanism regulation changes in TGF-β / Smad signaling pathway under the influence of astragaloside IV. Therefore, we will pay close attention to relevant research results in real-time and design more research to make up for this deficiency.

To sum up, astragaloside IV plays an important role in improving cognitive dysfunction in rats with cerebral infarction while affecting the levels of TGF-β, Smad1, Smad3 and Smad7 and activating TGF-β / Smad signaling pathway.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
LL wrote the manuscript. YG and YZ were responsible for ELISA. JW and YJ contributed to the observation indexes analysis. The final version was read and adopted by all the authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Jinan Municipal No.2 Hospital of Traditional Chinese Medicine.

Consent for publication
Not applicable.

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

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