CENTRAL ASIAN JOURNAL of MEDICAL SCIENCES
CAJMS

Original Article

Cent Asian J Med Sci. 2021 March;7(1):23–28. https://doi.org/10.24079/CAJMS.2021.03.005

The Effect of Antischemin Preparations on Hypoxia

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Submitted: December 1, 2020
Revised: February 7, 2021
Accepted: March 9, 2020

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Objectives: We have aimed to determine the anti-hypoxic action of antischemin, an active anti-inflammatory drug that protects brain cells from damage and death during cerebral hemorrhage and hypoxia. **Methods:** We have studied antischemin made from *Astragalus membraneceus* roots, *Scutellaria baicalensis Georgi* roots, and *Gingko Biloba* leaves denizen in Mongolia and compared its protective effect against hypoxia compared to each of its constituents alone 6 groups of 8 mice. Normobaric hypoxia resistance as well as tissue hypoxia resistance was determined. **Results:** For antischemin preparation 100 mg/kg, the tolerance of normobaric hypoxia was 42 minutes or 47.2% higher in the treatment group ($p \leq 0.001$), and the latent period of hypoxia was increased by 22.7% ($p \leq 0.05$). The period of hypoxia increased 32% ($p \leq 0.001$). **Conclusions:** Antischemin has been shown to make tissue more resistant to hypoxia and and have more anti-hypoxic activity than its constituents alone.

Keywords: Hypoxia, Pathology, Blood, Mongolia

Introduction

Recently, the action of active synthetic and natural compounds in the prevention and treatment of ischemia and hypoxia in organs with high oxygen demand and relatively high metabolic rate, such as the brain and heart, have been extensively studied [1]. The brain is one of the most metabolically active organs with a relatively high need for oxygen and glucose. Although it comprises only 2% of a person's body weight, the brain consumes 20% of the total oxygen entering the body and 2% of all glucose, even although it does not produce any mechanical work or sizable volumes of secretions [2]. On the other hand, the brain and heart are very sensitive to disruption of blood flow due to very low storage of energy and substrates [3-5].

The brain is a metabolically active organ, and it contains virtually no oxygen reserve. Therefore, during the occlusion of the brain circulation, local oxygen levels in the drop resulting in hypoxia and the metabolic processes that consume cellular energy can continue for 1-2 minutes only. Hypoxia typically occurs clinically when there is insufficient blood flow (cardiac arrest, cerebral hemorrhage etc.) or respiratory dysfunction. Hypoxia results in the production of nitric oxide, which in turn provokes lipid peroxidation and cell membrane injury and induces reactive oxygen species (ROS), which induce further damage. Numerous investigations, thus, have been done to prove the ROS scavenging ability of the plant extracts which gives them antihypoxia properties.

Some Chinese herbal medicines demonstrate antioxidant properties, produce increased cerebral blood flow, inhibit platelet aggregation, and increase tissue tolerance to hypoxia [6]. For example, Zhang et al. showed the hypoxia-induced nerve injury-reducing activity of YinxingDamo, which includes a Ginkgo extract. Further, it has been suggested that Tongxinluo capsules that contain ginseng and hirudo extracts protect nerve cells by increasing the expression of brain-derived neurotrophic factors [7]. The study by Xue et al. demonstrated that angelica polysaccharide plays important in anti-apoptotic and anti-inflammatory roles in LPS-evoked excessive inflammation and apoptosis process in PC12 cells [8]. Also, the angelica polysaccharide has potential functions in protecting rat cardiomyocyte H9c2 cells from hypoxia-stimulated inflammatory injury via regulating miR-22 [9-11]. Kamikihi-To is a traditional Chinese medicine that consists of the following 14 herbs: *Astragalus, Ginseng, Atractylodes, Hoelen, Poly gala, Jujube, Longan, Zizyphus, Angelica, Licorice, Ginger, Saussurea, Bupleurum* and *Gardenia*. Various studies of Kamikihi-To's constituents report that Astragalus includes aminobutyric acid, which improves cerebral circulation and metabolism, while *Ginseng* and *Angelica* inhibit platelet aggregation. Nishizawa et al. investigated Kamikihi-To's effect against cerebral ischemia, hypoxia and anoxia in mice and gerbils. They confirmed that Kamikihi-Ko may have protective effects against cerebral ischemic disorders [12]. Further, Liu et al. demonstrated that Buyanghuanwutang (BYHWT), a popular traditional Chinese medicine formula, can delay hypoxic-ischemic encephalopathy onset and preserve motor function, primarily by regulating inflammation, apoptosis and inhibition by mediating JNK signaling [13]. This decoction consists of seven herbal medicines which include *Astragalus membranaceus, Angelica sinensis, Paeonia lactiflora, Ligusticum chuanxiong Hort, Carthamus tinctorius, Amygdalus persica* and *Pheretima aspergillum*. All of these components are listed in the Chinese Pharmacopoeia, and have been shown to have a neuroprotective effect for conditions such as brain ischemia, stroke-induced disability, and cerebral ischemia-reperfusion injury.

Antischemin preparation is a comprised of a extract from the leaves of three plants found in Mongolia: *Astragalus membraneceus* roots, *Scutellaria baicalensis Georgi* roots, and *Gingko Biloba* leaves. Previous studies of antischemin's effect on blood lipids have confirmed that antishemin reduce cholesterol, triglycerides and low-density lipoprotein levels while increasing high-density lipoprotein level up to 19% during acute and chronic cerebral ischemic disease [6]. Further, Oyuntsetseg et al. demonstrated that antischemin inhibits lipid peroxidation and has protective effects preventing neuron degradation and necrosis in induced brain ischemia in a rat model [7].

The objective of this study is to determine the protective effect of antischemin on brain cells and hypoxia and compare these results to antischemin's constituents alone and *Ginko Bilobil* (hereafter called Bilobil to avoid confusion with *Gingko Bilobi*).

Materials and Methods

Study design

Forty-eight Vistar mice weighing 20-25g were divided into 6 groups of 8 subjects according to age, sex, and body weight. The 6 groups received different oral treatments.

The control group received distilled water a dose of 40 mg/kg and the antischemin group received antischemin 100 mg/kg. The 3 groups receiving the antischemin constiuents alone received were as follows: the *Astragalus membraneceus* group received a 1:10 dilution of *Astragalus membraneceus* 160 mg/kg; the *Scutellaria baicalensis Georgi* group received a 1:5 dilution of *Scutellaria baicalensis Georgi* 160 mg/kg; and the *Ginkgo Scutellaria baicalensis Georgi* group received a 1:10 dilution of the *Ginkgo Scutellaria baicalensis Georgi* 160 mg/kg. Lastly, a because *Bilobil* is often recommended to a group treated with *Bilobil* at 40 mg/kg was included as comparison. For each group, normobaric hypoxia was then chemically induced by injecting sodium nitroprusside, which produces nitric oxide and in high doses inhibits bloods ability to transport oxygen. As the tissue hypoxia rapidly progresses over time, the animals experience convulsions, followed by respiratory arrest and the time between infusion and these events were recorded.

The research was conducted on a control-trail study based on the "Research and Innovation Center" of the New Medicine University. The study used the roots of *Astragalus membraneceus, Scutellaria baicalensis Georgi*, and *Gingko Biloba* leaves from in Mongolia.

Determination of hypoxia resistance

We used the methodology of Kulkarni [15] and Ulugol et al. [16] and of Zelenskaya et al. [17] were used to determine the normobaric hypoxia time, latent hypoxia duration, and the period of hypoxia. Briefly, the animals were weighed and rectal temperatures were measured. Ten minutes before inducing hypoxia, the rectal temperatures were taken again. Hypoxia was established with the IV infusion of nitroprusside 25 mg/kg. The time between the infusion and the first convulsion was recorded. The time between the infusion and respiratory arrest was recorded. The difference between these two times was recorded.

Statistical analysis

The average value of continuous variables which are the tolerability of normobaric hypoxia, the latent hypoxia duration and the period of hypoxia in the control, antischemin, a*stragalus membranaceus, scutellaria baicalensis, gingko biloba* and *bilobil* groups were compared using Kruskal-Wallis test. Multiple comparisons between the control group and study groups were made using Wilcoxon signed-rank test. Significant values have been adjusted by the Bonferroni correction for multiple comparison tests. A critical p-value of < 0.05 was used. SPSS version 24 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethical statement

Ethical approval was obtained from the Ethical Review Committee of Mongolian National University of Medical Sciences (Protocol No.2019/3-07). All efforts were made to minimize the number of animals used and their suffering.

Results

The tolerability of normobaric hypoxia

As shown in Table 1, the tolerability of normobaric hypoxia in the control group animals was 47 ± 3.44 min. In this group, the tolerance of normobaric hypoxia was 47 ± 3.44 minutes or 47.2% higher (89 ± 6.20 min) compared to that in control group ($p = 0.001$). On the other hand, the tolerance values for the *Astragalus membraneceus* group was 62 ± 4.63 min in compared to 67 ± 5.38 min in the *Scutellaria baicalensis* group ($p = 0.014$), and 76 ± 6.11 min in the *Gingko Biloba* group ($p = 0.024$), respectively. These values indicate that the tolerance of normobaric hypoxia increased by 10 ± 2.41 to 47 ± 3.44 minutes in the mice treated with *Astragalus membraneceus, Scutellaria baicalensis Georgi*, and *Gingko Biloba.*

Table 6. The effect of antischemin and an active anti-inflammatory drugs on the tolerability of normobaric hypoxia.

	Control (n=8)	Antischemin[a] (n=8)	*Astragalus membranaceus*[be] (n=8)	*Scutellaria baicalensis*[c] (n=8)	*Gingko Biloba*[d] (n=8)	Bilobil[e] (n=8)	*p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
The tolerability of normobaric hypoxia (minutes)	47 ± 3.44	89 ± 6.20	62 ± 4.63	67 ± 5.38	76 ± 6.11	72 ± 5.38	0.003

*Kruskal-Wallis test; [a]control vs. antischemin , $p < 0.001$; [b]control vs. astragalus, $p < 0.052$; [c]control vs. scutellaria, $p < 0.014$; [d]control vs. gingko, $p < 0.024$; [e]astragalus vs. bilobil, $p < 0.053$.

Compared with the groups receiving a single extract, the normobaric hypoxia time for the antischemin preparation was 27± 2.14 minutes higher than that in *Astragalus membraneceus* (p = 0.053) and approximately 22± 2.01 minutes higher than *Scutellaria baicalensis* extract (p = 0.024). Moreover, our result revealed that the tolerability of the antischemin preparation was better than in the comparative group, or group. It increased by 17 ± 1.48 minutes from that in group (72 ± 5.38 min, p < 0.001).

Table 2. The effect of antischemin and an active anti-inflammatory drugs on the latent hypoxia duration.

	Control (n=8)	Antischemin[a] (n=8)	*Astragalus membranaceus*[d] (n=8)	*Scutellaria baicalensis*[b] (n=8)	*Gingko Biloba*[c] (n=8)	Bilobil[d] (n=8)	*p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
The latent hypoxia duration (minutes)	75.08±8.75	97.2±9.04	82.29±8.67	79.33±8.12	92.15±9.08	96.3±9.54	0.043

*Kruskal-Wallis test; [a]control vs. antischemin , p < 0.023; [b]control vs. scutellaria, p < 0.041; [c]control vs. gingko, p < 0.025; [d]astragalus vs. bilobil, p < 0.056.

The resistance of tissue hypoxia with Antischemin

We compared the resistance of tissue hypoxia in antischemin in each group of animals. As shown in Table 2, our results show that the latent period of hypoxia increased in the group who received antischemin by 22.7% (97.2 ± 9.04 min) compared to the control group (75.08 ±8.75 min, p = 0.023). In the *Astragalus membraneceus*-treated group, the tolerability increased by 8.7% (82.29 ± 8.67 minutes, p = 0.056), in the *Scutellaria baicalensis Georgi* group by 5.3% (79.33±8.12 minutes, p = 0.041), and in the *Gingko Biloba* group it increased by 18.5% (92.15±9.08 minutes, p = 0.025) compared to the control group (75.08 ±8.75 min). When compared to the antischemin preparation group the latent hypoxia duration was slightly longer than that in group (97.2 ± 9.04 vs. 96.3 ± 9.54 minutes, p = 0.023).

Table 3. The effect of antischemin and an active anti-inflammatory drugs on during the period of hypoxia.

	Control (n=8)	Antischemin[b] (n=8)	*Astragalus membranaceus*[d] (n=8)	*Scutellaria baicalensis*[a] (n=8)	*Gingko Biloba*[e] (n=8)	Bilobil[c] (n=8)	*p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
During the period of hypoxia (minutes)	95.26±11.45	140.2±12.65	124.0±10.4[d]	119.4±10.5[a]	102.68±9.46	131.5±12.8	0.000

*Kruskal-Wallis test; [a]control vs. scutellaria, p < 0.030; [b]control vs. antischemin, p < 0.035; [c]control vs. bilobil, p < 0.002; [d]control vs. astragalus, p < 0.045; [e]control vs. gingko, p < 0.003.

Table 3 shows duration of hypoxia in the different groups. The control group's duration of hypoxia was 95.26 ± 11.45 minutes, while the antischemin group's was 32% longer (140.2 ± 12.65 minutes, p = 0.023). Compared the control group, the to duration of hypoxia of *Astragalus membraneceus*-treated group' was 23.1% higher (124.0±10.4 minutes, p = 0.056), and the *Scutellaria baicalensis Georgi* group was 20.2 % more (119.4 ± 10.5 minutes, p = 0.041). Compared to the control, the *Gingko Biloba* group the hypoxia duration was significantly different (102.68±9.46 minutes, p = 0.025). In the group, the duration was increased by 27.5% (131.5 ± 12.8 minutes) compared to that in the control group (p = 0.056). We found that the duration of the hypoxia of the antischemin group was prolonged approximately 38 ± 3.51 minutes more than mice treated with *Gingko Biloba* extracts, and 21± 2.85 minutes than the animals treated with *Scutellaria baicalensis Georgi* extracts, alone.

Discussion

We desire to develop low-cost drugs that are active in preventing and treating cell wall-energy metabolism disorders in vital organs such as cerebral ischemia, brain, and heart, compared to those that are imported to Mongolia at high prices. Other researchers have found that "Antischemin" preparation, which includes *Astragalus membraneceus, Scutellaria baicalensis Georgi*, and *Gingko Biloba* acts as antioxidants [12], sedatives [13-15], anticoagulatiants [16], liver protectants [17], anti-allergic [18], anti-neoplastic [19, 20], anti-cerebral ischemia and hypoxic [21, 22], antibacterial [23], antiviral [24], anti-inflammatory [25, 26], and antihypertensive effects.

The use of medicinal herbs on hypoxia or cerebral ischemia injury has been studied by others. Zheng et al. demonstrated that pre-treatment with *Astragalus* polysaccharides upregulates

miR-138 in hypoxia-injured rat stem cells. The polysaccharides attenuated the cell injury induced by hypoxia and enhanced expression of anti-apoptotic factors [22]. Moreover, in the study of the chronic hypoxia model rats, astragaloside IV, a high-purity drug extracted from *Astragalus membranaceus*, which reportedly is a widely used herb in China, significantly decreased the mean pulmonary arterial pressure as well as the right ventricular pressure [23]. On the other hand, there has been much research on how *Ginkgo Biloba* extract improves oxidation and microcirculation. Cho et al. studied the protective effect of *Ginkgo Biloba* on neurons in rats by producing hypoxia in retinal ganglion cells in vitro and in vivo. They found that in vitro significantly reduced necrosis of retinal ganglion cells and that the effect was dose-dependent. The *Ginkgo Biloba* extract, in both in vitro and in vivo studies, has a proven protective role of retinal ganglion cells because of its anti-hypoxic effects [5].

We confirmed that during the period of hypoxia was 7.2-32% longer in the groups that received *Astragalus membraneceus, Scutellaria baicalensis Georgi* and *Gingko Biloba* alone, compared to the control group. Moreover, the latent hypoxia duration was 5.3-22.7% longer in these treatments compared to the controls. The tolerability of normobaric hypoxia was also 24 - 47% longer in the treatment group that received *Astragalus membraneceus* (1:5), *Scutellaria baicalensis Georgi* (1:5) and *Gingko Biloba* (1:10), compared to the control group. In addition, the drug which has a ingredient of gingko biloba inhibits the formation of peroxynitrite (ONOO—), which is a powerful oxidant that can damage a wide array of molecules in cells, including DNA and proteins, at the site of ischemia and hypoxia. Therefore, this drug reduces the intensity of fat oxidation, which foreign researchers has been verified. Antischemin protects the brain from ischemia, hypoxia, and oxidative stress caused by superoxide anions, hydroxyls, and nitroxides. It is reasonable to assume that the combination of flavonoids, polyphenolic compounds and turpentine saponins in each of its three constituent plants has many biologically active compounds. Further, Fitzl et al. also demonstrated that *Gingko Biloba* extract can be protective against acute hypoxia in rat myocardium [24, 26]. After hypoxia, the functional capacity associated with MI amounted only to 46% of the normal and was improved by *Gingko Biloba* extracts to 53%. In all animal groups in our study except the anitischemin group, the duration was 95.26 ± 11.45 minutes, and in the group received that antischemin 100 mg/kg the period of hypoxia increased 32% (140.2 ± 12.65 minutes).

Our study has some limitations. We were unable to determine the exact compound which had the decreased the effect of hypoxia. Therefore, the potential molecular mechanism of the antischemin's protective effect against hypoxia requires further elucidation. Further, for the future clinical applications of the antischemin preparations, we need to perform experiments with different doses and perform toxicology studies to ensure the antischemin is safe at the dose required to antioxidant effect. Further, it is required to develop new generations of these compounds to improve their neuroprotective effects. Further research is necessary to provide new alternatives in the implementation of new therapeutic strategies and novel approaches.

Conclusion

Antischemin treated animals were more resistant to tissue hypoxia and had better anti-hypoxic activity than other treatments. We determined that the antischemin preparation has anti-hypoxic effects.

Conflict of Interest

The authors declare no conflict of interests.

Acknowledgements

We are grateful to our study consultant ScD, professor Ambaga.M, who helped to conduct our study, supervisor of our study ScD, professor Sarantsetseg.B, supervisor of our study PhD, professor Khishigjargal.S, doctoral student Ariuntsetseg.B, Enebish.B, Munkhbayar.S, Jigjidnorov.M, employees of Research-Innovation center of "New Medicine" medical University, "Bio-design laboratory".

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