Comparative Characteristics of Antidepressant, Anti-Hypoxic Action and Effect on the Physical Endurance of *Scutellaria baicalensis* Drugs

Matviychuk A.V. Slipchenko G.D., Stoletov Y.V., Belik G. V., Ruban O.A., Kutsenko S.A.

National University of Pharmacy, Kharkov, Ukraine

The influence of original drugs from *Scutellaria baicalensis* Georgi (Dry extract, powder of rhizomes and roots, tablets "Scutex" on the basis of the dry extract and capsules "Scutella" containing powder of rhizomes with roots) has been studied on the depressive behavior, physical endurance and anti-hypoxic activity in mice. The experiments have revealed that dry extract of *S. baicalensis* has the antidepressant action.

Powder from rhizomes and roots of *S. baicalensis* and capsules "Scutella" has anti-hypoxic action. All test drugs showed no influence on physical endurance of mice. These results suggest that the using of the dry extract of *S. baicalensis* as an antidepressant drug, and rhizomes with roots and capsules "Scutella" as an anti-hypoxic remedy.

Key words: *Scutellaria baicalensis*, antidepressive action, physical endurance, anti-hypoxic activity.

SCUTELLARIA BAICALENSIS (ÇİN TAKKESİ) İLAÇLARININ ANTİ-DEPRESAN, ANTİ-HİPOKSİK VE FİZİKSEL DAYANIKLILIGA KARŞI ETKİLERİNİN KARŞILAŞTIRMALI ÖZELLIKLERİ.

Orjinal *Scutellaria baicalensis* Georgi ilaçlarının (kuru ekstresi, rizom ve kök tozları, "Scutex" tabletlerinin kuru ekstresi ve rizom ve kök tozu taşıyan "Scutella" kapsülleri) depresif davranış, fiziksel dayanıklılık ve antihipoksik aktiviteleri fareler üzerinde test edilmiştir. Deneyler, *S. baicalensis*'in kuru ekstraktının antidepresan etkiye sahip olduğunu ortaya koymuştur.

S. baicalensis'in rizom ve köklerinden elde edilen toz ve "Scutella" kapsüllerinin anti-hipoksik etkili olduğu görülmüştür. Hiçbir test ilacı farelerin fiziksel dayanma gücü üzerinde herhangi bir etki göstermemiştir. Bu sonuçlar, *S. baicalensis*'in kuru ekstraktının antidepresan ilaç ve köklü rizomların ve "Scutella" kapsüllerinin anti-hipoksik ilaç olarak kullanımını önermektedir.

Anahtar kelimeler: *Scutellaria baicalensis*, anti-depresan etki, fiziksel dayanıklılık, antihipoksik aktivite

Corespondence: e mail:galinaslipchenko@ukr.net, Phone:+380957355942

INTRODUCTION

Creation of new effective drugs based on plant material is relevant and a priority direction of modern pharmacy. Herbal origin preparations have recently become very popular due to the variety of therapeutic effects, provided by both individual substances and complex compounds found in plant material.

Scutellaria baicalensis Georgi (SB) (Lamiaceae) is a promising source of biologically active substances. The main biologically active substance of SB are flavonoids and flavonoid glycosides such as baicalin, baicalein, scutellarin, oroxylin, wogonin, apigenin and others.

In Chinese medicine roots of SB has long been used for hypertension, epilepsy, nervousness, sleep disorders traditionally. Recently is being investigated psychotropic and cerebroprotective action of SB drugs, including in neurodegenerative diseases, CNS lesions of ischemic genesis.[1-6] It has been proved that preparations of SB raw (dry extract, tablets of "Scutex" and capsules of "Scutella") show anxiolytic, anti-amnestic effect.[7,8] In view of the above apparent becomes the expediency of comprehensive comprative pharmacological study of SB dry extract, powder of roots and rhizomes of SB and preparations based on them as potential psychotropic drugs.

The purpose of the work is to evaluate the possible antidepressant properties, anti-hypoxic action of dry extract, powder of roots and rhizomes of SB and also tablets "Scutex" based on SBDE and hard gelatin capsules "Scutella" containing powder of rhizomes with roots of SB on physical endurance of mice.

MATERIALS AND METHODS

Used SBDE (dry extract *Scutellaria baicalensis*), powder of roots and rhizomes from SB (SBRP), tablets from dry extract of SB codenamed "Scutex" and hard gelatin capsules from the crushed root of SB codenamed "Scutella" were obtained from NUPh's Department of industrial technology of drugs.

In the experiment 94 random-breed white male mice weighing 20-29g were used and kept in standard sanitary and laboratory conditions. During the experiments, the animals were in the vivarium at 19-24ºC, humidity was under 50%, natural light mode was "day-night" in plastic cages on a standard diet. Experimental studies have been performed in accordance with the "general ethical principles of animal experiments" (Ukraine, 2001) in accordance with the "European Convention

for the Protection of vertebrate animals used for experimental and other scientific purposes".

SBDE was used in doses of 25 mg/kg, 50 mg / kg, 75 mg/kg; SBRP was used in doses of 87 mg/kg (25 mg/kg in terms of baicalin), 173 mg/kg (50 mg/kg in terms of baicalin) and 260 mg/kg (75 mg/kg in terms of baicalin); tablets of codenamed "Scutex" and hard gelatin capsules codenamed "Scutella" were used in doses of 320 mg/kg (50 mg/kg in terms of baicalin) and 260 mg/kg (75 mg/kg in terms of baicalin) respectively. SBDE, SBRP, crushed tablet mass "Scutex" and the contents of the capsules "Scutella" were dissolved in water and entered into mice through intragastric probe (ig) in a volume of 0.1 ml for 10 g mass once per day for 5-8 days last 30-60 minutes before experiment. Control group injected with the same amount of pooled tap water. The reference product - "Bilobil" (KRKA, Slovenia) at a dose of 100 mg/kg, was dissolved in water and injected in the same mode[9]. All behavioral tests were carried out sequentially, synchronously with the appropriate control, because the effects depend on chronopharmacological factor.

Study of antidepressant properties of SBDE, SBRP, "Scutex" and "Scutella" drugs and reference drug conducted by mice tail suspension test (despair behavior).[10] Antihypoxic effect was evaluated on the model of normobaric hypoxic hypoxia with hypercapnia.[11] The impact of the studied substances on the physical endurance of mice was studied by a test of swimming with the load.[10] The results were treated statistically using STATISTICA 8.0 software by evaluating the reliability of differences between comparison groups by parametric Student's criterion (t) in the cases of normal distribution, nonparametric Mann-Whitney criterion (U) in its absence. The difference was considered statistically significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Results of antidepressant activity the SBDE in terms of immobilization test (tail suspension test) are shown in Table 1.

The obtained results indicate that SBDE at a dose of 50 mg/kg increases latent time of freezed mice hanging 1.7 times or by 68 % compared to control ($p \leq 0,05$); amount of freezed hangs has decreased in 1.2 times or by 18 %; overall length of freezed hangs decreased 1.5 times or by 35 % ($p \leq 0,05$). Reference drug "Bilobil"

in a dose of 100 mg/kg increased latency time of freezed hangs in 1.4 times or by 39 % ($p \leq 0,05$), and total time of freezed hangs tendentiously decreased 1.2 times.

Table 1. Influence of SBDE and reference drug "Bilobil" on despair behavior in mice immobilization test conditions (tail suspension test)

Group, dose, n,	Latent time of freeze hanging, s	Number of freezed hangs	Total duration of freezed hangs, s
Control (1), n = 6	42,8 ± 3,70	13,5 ± 1,60	108,7 ± 7,00
"Bilobil" 1, 100 mg/kg, n = 6	59,5 ± 5,70 *	13,5 ± 2,00	93,3 ± 6,00
SBDE, 50 mg/kg, n = 9	71,9 ± 5,90 *	11,1 ± 2,00	70,6 ± 5,50 *
Control (2), n = 8	42,13 ± 12,73	11,25 ± 1,29	108,13 ± 18,85
"Bilobil" (2), 100 mg/kg, n = 7	34,14 ± 6,75	11,43 ± 0,87	128,14 ± 9,69
SBRP, 173 mg/kg, n=7	98,43 ± 28,82	7,71 ± 1,58	93 ± 20,22
SBRP, 260 mg/kg, n=7	63,14 ± 9,04	8 ± 0,72	102,29 ± 8,90
Control (3), n = 6	35,50 ± 5,81	10,67 ± 1,36	103,83 ± 20,6
"Bilobil" (3), 100 mg/kg, n = 6	54,00 ± 13,50	12,67 ± 1,61	103,67 ± 16,01
"Scutex", 320 mg/kg, n = 6	102,33 ± 40,18	7,50 ± 2,55	58,0 ± 19,04
Control (4), n = 7	41,30 ± 6,13	12,35 ± 0,98	111,84 ± 22,6
"Bilobil" (4), 100 mg/kg, n = 6	52,22 ± 10,11	12,71 ± 1,25	101,22 ± 17,5
"Scutella", 260 mg/kg, n = 6	55,42 ± 12,05	9,13 ± 1,18	104,17 ± 19,04

Notes: s – seconds; mg/kg – milligrams of drug per kilogram of animal weight;

* - Statistically significant differences ($p \leq 0,05$ as for appropriate control.

Action of SBDE exceeded the effect of reference drug "Bilobil" 1.2 times by increase in latency for freezed hangs. So SBDE possesses antidepressant action.

The next step was to study the antidepressant activity of SBRP in doses of 173 mg/kg and 260 mg/kg. SBRP in both doses has no significant effect on quantitative parameters of depressive behavior (Table 1). "Scutex" tablets and "Scutella" capsules also do not show probable antidepressant activity (Table 1). They only biased increased latent time of freeze hangings and reduced their total duration. On the other hand *Ginkgo biloba* ("Bilobil") the drug, the effect on depressive behavior is weak and unstable, as in the different series of experiments it either increased latency time of immobilization or tendentiionally reduced its total duration, or had no significant effect.

All drugs of SB- SBDE, SBRP, "Scutex" tablets, "Scutella" capsules as well as "Bilobil" did not affect the physical endurance of mice in the test of swimming to exhaustion (Table 2). This is evidenced by the unchanged swimming time compared with the control.

Table 2. The impact of SB drugs and reference drug "Bilobil" on physical endurance of mice by swimming with load test

Group, dose, n	Time of swimming to exhaustion, min
Control (1)	3,44 ± 0,33
SBDE, 50 mg/kg	3,41 ± 0,34
"Bilobil" (1), 100 mg/kg	3,40 ± 0,27
Control (2)	6,01 ± 0,50
SBRP, 173 mg/kg	7,92 ± 0,91
SBRP, 260 mg/kg	6,73 ± 0,75
"Bilobil" (2), 100 mg/kg	6,05 ± 0,42
Control (3)	3,60 ± 0,23
"Scutex" 320 mg/kg	3,64 ± 0,20
"Bilobil" (3), 100 mg kg	3,68 ± 0,43
Control (4)	5,81 ± 0,52
Scutella, 260 mg/kg	6,15 ± 0,56
"Bilobil" 100 mg/kg	6,26 ± 0,42

Notes: All values are mean ± standard deviations of six experiments.

Results of the study on anti-hypoxic properties of SBDE on normobaric hypoxic hypoxia with hypercapnia model demonstrate increased life expectancy of mice 1.3 times compared to the control (Table.3), indicating a distinct antihypoxic effect of the drug. In the group of animals treated with the comparator, statistically significant differences with control were not observed.

SBRP at a dose of 173 mg/kg significantly increased the life duration of mice by 1.3 times compared to the control. Similar results were observed when administered reference drug "Bilobil." Influenced by SBRP at a dose of 260 mg/kg lifespan of mice increased 1.6 times compared with the control, that is 33 % more than in the background of SBRP at a dose of 173 mg/kg (Table 3)

Table 3. Impact of SBDE, SBRP, "Scutex", "Scutella" and "Bilobil" on life expectancy in mice under normobaric hypoxic hypoxia with hypercapnia

Group, dose, n	Life span, min
Control (1), n = 8	24,47 ± 1,67
SBDE, 50 mg/kg, n=8	32,03 ± 2,18 *
"Bilobil" (1), 100 mg/kg, n = 6	30,07 ± 4,14
Control (2), n = 8	23,62 ± 1,11
SBRP, 173 mg/kg, n=6	30,87 ± 3,17 *
SBRP, 260 mg/kg, n=7	38,73 ± 3,79 *#
"Bilobil" (2), 100 mg/kg, n = 7	30,96 ± 1,49 *
Control (3), n = 6	17,89 ± 0,60
"Scutex" 320 mg/kg, n = 6	21,81 ± 2,36
"Bilobil", 100 mg/kg, n = 5	20,27 ± 1,06
Control (4), n = 7	22,77 ± 0,84 *
Scutella, 260 mg/kg, n = 6	36,99 ± 3,98
"Bilobil" (4), 100 mg/kg, n = 6	29,96 ± 1,31 *

Notes: mg/kg – milligrams of drug per kilogram of animal weight. All values are mean ± standard deviations; number of experiments for each group is mentioned in the Table; * - Significant differences from control indicator of corresponding series of experiments ($p < 0,05$); # - Significant differences with the rate of animals treated with "Bilobil" ($p < 0,05$), in the corresponding series of experiments.

So SBRP at a dose of 260 mg/kg has the most significant antihypoxic effect in terms of normobaric hypoxic hypoxia with hypercapnia and exceeds the effect of comparison drug, and at a dose of 173 mg/kg SBRP acts at the level of reference drug.

"Scutex" tablets have only shown the tend to increase life duration of mice by 21.9 % compared with the control. "Bilobil" comparator has also showed a tendency to increase lifespan of mice by 13.3 % compared to the control group.

"Scutella" capsules (Table.3) significantly increase the lifespan of mice by 1.6 times compared to the control. Under the influence of "Bilobil" also there was an increase in life expectancy of mice in 1.3 times compared to the control group. Thus, we can conclude that "Scutella" reveals antihypoxic action and has advantage over the reference "Bilobil" drug. Antihypoxic effect of the latter is not stable, because in different experiments it is revealed either on a statistically significant level, or biased.

CONCLUSIONS

SBDE at a dose 50 mg/kg shows antidepressant activity which exceeds the activity of the comparison drug "Bilobil". SBRP at doses 173 mg/kg and 260 mg/kg does not show antidepressant action, as well as tablets "Scutex" and capsules "Scutella."

SBDE, SBRP, tablets "Scutex" and capsules "Scutella" do not affect the physical endurance of mice.

SBDE at a dose 50 mg/kg and SBRP at a dose of 173 mg/kg and 260 mg/kg exhibit antihypoxic activity exceeding the activity of the reference drug "Bilobil." "Scutex" tablets show no antihypoxic action and "Scutella" capsules cause probable antihypoxic action that exceeds the effect of the reference drug "Bilobil".

REFERENCES

1. Yakovleva GP, Blinova KF. Encyclopedic Dictionary of medicinal plants and products of animal origin. Belodubovskaya GA, Zabinkova NN, eds. Utchebnaja kniga. St. Petersburg; 1999:1-407.
2. Ibrahimova VS. Chinese medicine. Methods of diagnosis and treatment. Pharmaceuticals. Acupuncture therapy. Antares; 1994:426-429.

3. Arnal-Shnebellen B, Goetz P Encyclopedia of medicinal plants (translated from French). Grassar E., Yunen M., eds. Riderz Daydzhest; 2004;1-352
4. Shang Y, Zhang H, Cheng J, Miao H, Liu Y, Cao K, Wang H. Flavonoids from *Scutellaria baicalensis* Georgi are effective to treat cerebral ischemia/reperfusion. Neural Regen Res. 2013;8(6):514-522.
5. Lu JH, Ardah MT, Durairajan SS, Liu LF, Xie LX, Fong WF, Hasan MY, Huang JD, El-Agnaf OM, Li M. Baicalein inhibits formation of α-synuclein oligomers within living cells and prevents Aβ peptide fibrillation and oligomerisation. Chembiochem. 2011;12(4):615-624.
6. Xiong Z, Jiang B, Wu PF, Tian J, Shi LL, Gu J, Hu ZL, Fu H, Wang F, Chen JG. Antidepressant effects of a plant-derived flavonoid baicalein involving extracellular signal-regulated kinases cascade. Biol Pharm Bull. 2011;34(2):253-259.
7. Slipchenko GD, Shtrygol' S.Yu, Kudina OV, Taran AV, Ruban OA. The comparative pre-clinical study of psychotropic properties of the medicines from *Scutellaria baicalensis* Georgi. Pharmacology and Drug Toxycology. 2016;4-5:41-49.
8. Shtrygol' S.Yu., Slipchenko GD, Kudinov AV, Matviichuk AV, Ruban OA. Comparative clinical trials of antiamnestic properties of *Scutellaria baicalensis* drugs. Phitoterapiya Chasopis. 2016;4:17-20.
9. Tsyvunin VV, Shtrygol' S.Yu., Prokopenko Yu.S. Neuroprotective properties of dry extracts of *Fumaria schleicheri* and *Ocimum basilicum*. Reviews on clinical pharmacology and drug therapy. 2013;11(3):66-71.
10. Stefanov OV. Preclinical study of drugs (1st ed). Kyiv; Avitsena; 2001:1-528.
11. Mironov AN, ed. Guidance on conducting the preclinical studies of pharmaceuticals(1st ed) Moscow; Griff & Co.; 2012:1-944.