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INVOLVEMENT OF THE GABA-ERGIC SYSTEM IN ANXIOLYTIC- AND ANTIDEPRESSIVE EFFECTS OF THE *SCROPHULARIA STRIATA* EXTRACT IN RATS

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Recently, neuroprotective and anti-inflammatory effects of an extract of *Scrophularia striata* Boiss (*Sc. st.*) (*Scrophulariaceae*) were shown in rodents. In our study, we investigated the effects of the *Sc. st.* extract on anxiety and depression-like behaviors in rats and tried to find possible mechanisms responsible for these influences. The elevated plus-maze (EPM) and forced swimming test (FST) were used. The ethanol extract of *Sc. st.* was perorally administered at different doses (20, 50, 100, 160, and 220 mg/kg). We also assessed interaction between the effective doses of *Sc. st.* and $GABA_A$ receptors in the brain. It was found that *Sc. st.* at doses of 100 and 160 mg/kg increased normalized values of the open arm time and number of entries in the EPM and decreased the immobility time in the FST in comparison with the control group, indicating anxiolytic and antidepression effects, respectively. Intracerebroventricular administrations of a $GABA_A$ receptor agonist, muscimol (0.5, 0.75, and 1 μg/rat), enhanced the respective *Sc. st.* effects, while a $GABA_A$ receptor antagonist, bicuculline (0.5, 1 and 2 μg/rat), blocked these effects. Thus, anxiolytic and antidepressive effects of the active components of *Sc. st.* may be mediated by modulation of the GABAergic system.

Keywords: *Scrophularia striata*, anxiety, depression, elevated plus-maze, forced swimming test, GABA.

INTRODUCTION

Neuropsychiatric disorders, like anxiety and depression, are common causes of a reduced quality of life and, especially, of impaired functioning in aged subjects [1]. Recent studies showed that increased levels and severity of anxiety and depression in humans and animals can be associated with inflammatory processes in the brain [2, 3].

It is well known that various neurotransmitter systems, in particular serotonergic, GABA-ergic, dopaminergic, and glutamatergic ones, are significantly involved in the regulation and modulation of anxiety and depression-like behaviors at molecular levels of the brain structures [4-7]. Moreover, recent studies have provided substantial evidence that pharmacoactive components of certain herbal medicines can effectively modulate the state of different neurotransmitter systems in rodents [8].

GABA is an amino acid that acts as the main inhibitory neurotransmitter in the CNS through different receptor sites, classified as $GABA_A$, $GABA_B$, and $GABA_C$ receptors [9]. The involvement of $GABA_A$ receptors in the regulation of anxiety and depression has been the subject of extensive laboratory and clinical studies. It is well known that GABA-ergic agents and drugs demonstrate strong anxiolytic and antidepressive effects in humans and animals. Results of a number of clinical studies allowed researchers to believe that $GABA_A$ receptor protein is the main molecular target for anxiolytic drugs and antidepressants in anxiety and depression disorders [9].

Previous experimental studies have shown that an extract from *Scrophularia striata* Boiss (*Scrophulariacea,* figword*;* hereafter, *Sc. st.*) possesses significant neuroprotective and anti-inflammatory effects [10, 11]. A quercetin flavonoid was isolated from *Sc. st.* compounds by Monsef–Esfahani and colleagues [12]. Several studies demonstrated that

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this flavonoid exerts neuroprotective, anxiolytic, and antidepressive effects on laboratory animals [13-15].

In our study, we tried to evaluate the effects of the *Sc. st.* extract and possible mechanisms of the action of this drug in the elevated plus-maze and forced swimming tests (EPM and FST, respectively) in rats.

METHODS

Animals. Male Wistar rats (body mass 240-280 g) were purchased from the Pasteur Institute of Iran. The animals were individually housed in standard rat cages. The colony room was maintained under a 12/12-h light/dark cycle (light on at 07.00) at 23 ± 1°C and 50 ± 5% humidity. Animals were allowed unlimited access to food and water, except during the behavioral tests. All experiments were performed between 12.00 and 17.00 h, and each rat was tested only once. All stages of the study were performed using protocols approved by the Research and Ethics Committee of the Tabriz University of Medical Sciences and were conducted under the recommended conditions of the Guide for the Care and Use of Laboratory Animals of the National Institute of Health (NIH; Publication No. 85-23, revised 1985). Eight animals were used in each group of the experiments. All efforts were made to minimize animal suffering or discomfort and to reduce the number of animals used.

Plant Collection, Preparation of the Extract, and Its Administration. The aerial parts of *Sc. st.* were collected in January, 2011 in a Northwestern part of Iran (in the Ilam region) and dried at 30 ± 1°C. A sample was authenticated by M. Kosari-Nasab, and there was a voucher specimen of this plant at the Herbarium of the Tehran University (No. 36501). A total extract from *Sc. st.* was obtained as previously described [10]. The extract was dissolved in water and used at appropriate concentrations. Different groups of rats received peroral administrations of various doses of the *Sc. st.* extract (20, 50, 100, 160, or 220 mg/kg) or vehicle (equal volumes) consecutively for 12 days. The test sessions were performed 60 min after the last treatment.

Intracerebroventricular (i.c.v.) Injections of the Drugs Influencing GABA-ergic Effects. Muscimol and bicuculline (Sigma, USA) were used for i.c.v. injections in the experiments. Muscimol was dissolved in sterile 0.9% saline, while bicuculline was dissolved in a minimal volume of diluted acetic acid and then diluted to the required volume with vehicle. Control animals received saline or vehicle. Drug solutions were freshly prepared before administration.

Animals were allowed to adapt to the laboratory conditions for at least one week before surgery. They were i.p. anesthetized with 50 mg/kg ketamine hydrochloride + 4 mg/kg xylazine (Alfasan, Woerden, Holland) and placed in a stereotaxic instrument. Stainless steel guide cannulas (21-gauge) were stereotaxically implanted according to the following coordinates: AP –0.82 mm, ML +1.5 mm, and DV +2.0 mm related to the bregma [16]. The cannula was fixed to the skull with acrylic cement. The animals were then allowed 7 days before the test to recover from surgery and were handled about 4 min each day prior to behavioral testing (to minimize a nonspecific stress). The drugs mentioned above were injected with a Hamilton syringe through an internal cannula (27-gauge) terminating 1 mm below the tip of the guide into the right lateral cerebral ventricle over a 60-sec-long period. The inner cannula was left in place for additional 60 sec to allow diffusion of the solution and to reduce the possibility of a reflux. The injections were made 5 min before testing [17]

Different groups of rats received i.c.v. microinjections of the $GABA_A$ receptor agonist muscimol (0.5, 0.75, and 1.0 μg/rat). The other groups were injected with the $GABA_A$ receptor antagonist bicuculline (0.5, 1.0, and 2.0 μg/rat). These rats were compared with the vehicle control groups. The test session was performed 5 min after i.c.v. injections.

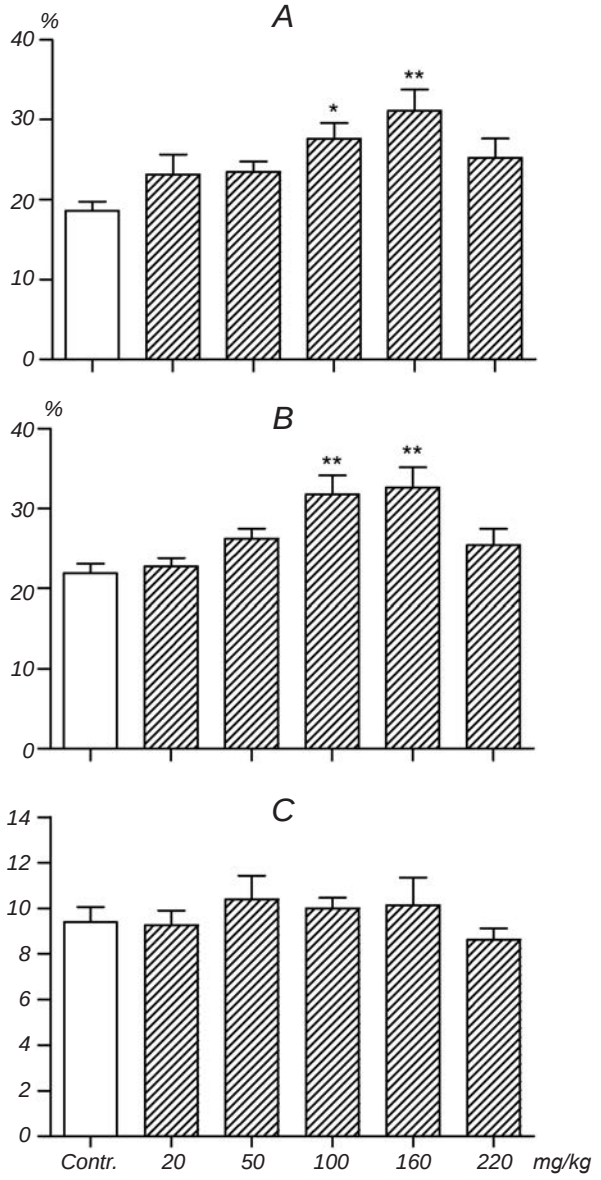
Elevated Plus-Maze (EPM) Test. The EPM was a plus-shaped apparatus constructed from wood and elevated to a 50 cm height above the floor. The apparatus with an open roof had a central platform (10 × 10 cm), two open arms (50 × 10 cm), and two equalized closed arms (50 × 10 × 50 cm) opposite to each other. Testing was performed in the center of a quiet and dimly lit room. The behavior data were collected by a "blind" observer using a mirror suspended above the EPM. Five minutes after the respective i.c.v. drug treatment, rats were placed individually at the center of the EPM, facing one of the open arms. The observer measured (i) time spent in the open arms, OAT, (ii) time spent in the closed arms, CAT, (iii) number of entries into the open arms, OAE, and (iv) number of entries into the closed arms, CAE, during 5-min-long test periods. An entry was defined as all four paws of the animal inside the arm. The EPM was cleaned with distilled water after each testing. The open-arm activity was quantified as an OAT value relative to the total time spent in any arm, and the OAE was normalized with

respect to the total number of entries into any arm; the data obtained were expressed as percentage. Total arm entries (OAE + CAE) were used as an index of the intensity of locomotor activity (LMA) [17, 18].

Forced Swimming Test (FST). Rats were individually placed into a transparent glass cylinder (height 80 cm, diameter 30 cm) filled for 40 cm with water maintained at 23 ± 1°C. The water was changed after each test. For the first exposure, rats were placed in the water for 15 min (pre-test session). Twenty-four hours later, animals were placed in the water cylinder again for a 5 min session (test session), and total duration of immobility within this time was measured. Each rat was judged to be immobile when it ceased struggling and remained floating motionless in the water and making only movements necessary to keep its head above the water. A decrease in the duration of immobility has been qualified as an index of the antidepressant-like effect [19].

Verification of the Cannula Position. At the end of the behavioral tests, each rat was euthanized by a chloroform overdose, and then 1 µl of a 1% methylene blue solution was injected i.c.v. as a marker of the injection site. Brains were removed after decapitation and fixed in a 10% formalin solution for at least 10 days. The brains were sliced, and the sites of injection were verified according to the atlas [16]. Data from animals with the injection sites located outside the ventricular region were not used in the analysis.

Statistics. All analyses were performed using IBM SPSS Statistics, version 20. Since the numerical data displayed the normal distribution and homogeneity of the variance, one-way ANOVA was used for comparison between the effects of different doses of drugs and those of vehicle. Two-way ANOVA was used for evaluation of interactions between drugs. Following a significant F value, *post hoc* analysis (Tukey's-test) was performed for assessing specific group comparisons. Differences with $P < 0.05$ between experimental groups at each point were considered statistically significant.



F i g. 1. Effects of peroral administration of different doses of an extract from *Scrophularia striata* or vehicle consecutively for 12 days on rat behavior in the elevated plus-maze test. Doses of the extract (20, 50, 100, 160, and 220 mg/kg) are shown below. Bars represent normalized means ± s.e.m. ($n = 8$) of open-arm time, % (A), open-arm entries, % (B), and indices of locomotor activity (C). $^{**}P < 0.01$ and $^{***}P < 0.001$, compared to the control (Contr.) group.

Р и с. 1. Впливи перорального введення екстракту *Scrophularia striata* в різних дозах або розчинника (протягом 12 днів) на поведінку щурів у піднятому лабіринті.

RESULTS

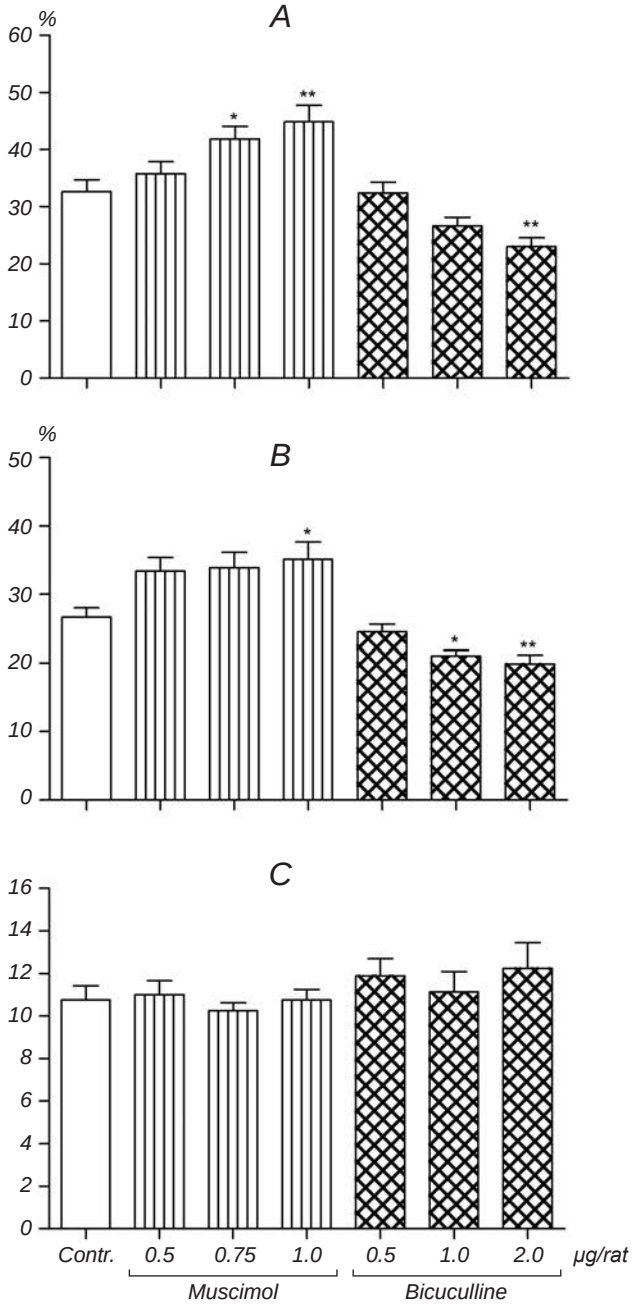
Effects of the *Sc. st.* Extract on Anxiety-Related Behavior in the EPM Test. Figure 1 shows the effects of oral administration of different doses of the *Sc. st.* extract or vehicle consecutively for 12 days. One-way ANOVA and *post hoc* analysis revealed that the effects of *Sc. st.* were significant at the doses of 100 and 160 mg/kg. Administrations of *Sc. st.* increased the OAT ($F_{(5, 42)} = 4.17$, $P < 0.005$) and OAE ($F_{(5, 42)} = 5.89$, $P < 0.001$) but did not significantly change LMA ($F_{(5, 42)} = 0.65$, $P > 0.05$). These data indicate that clear

anxiolytic effects are induced following administration of the *Sc. st.* extract in the medium doses used. Smaller doses of the extract provided only insignificant effects. The highest dose (220 mg/kg) exerted weaker effects on the OAT and OAE; a trend toward some suppression of LMA was observed in this group.

Effects of i.c.v. Injections of the $GABA_A$ Receptor Agonist and Antagonist on Anxiety Behavior in the EPM Test. Left segments of the panels in Fig. 2 illustrate the effects of i.c.v. injections of different doses of muscimol. A one-way ANOVA and *post hoc* analysis revealed that the effect of muscimol was significant at the dose of 1 μg/rat. Muscimol increased the OAT ($F_{(3, 28)} = 5.69$, $P < 0.005$) and OAE ($F_{(3, 28)} = 3.31$, $P < 0.04$), but induced no significant change in LMA ($F_{(3, 28)} = 0.31$, $P > 0.05$). These data indicate that clear anxiolytic effects were induced following i.c.v. administrations of the $GABA_A$ receptor agonist; the doses of 1.0 μg and, to a lesser, 0.75 μg were found to be effective.

However, rats i.c.v. infused with bicuculline (right segments of the panels in Fig. 2) showed significant decreases in the OAT ($F_{(3, 28)} = 6.93$, $P < 0.002$) and OAE ($F_{(3, 28)} = 6.91$, $P < 0.002$) at the dose of 2 μg/rat. The LMA changed insignificantly ($F_{(3, 28)} = 0.53$, $P > 0.05$). Thus, certain anxiogenic responses were observed following injections of the $GABA_A$ receptor antagonist in all doses used, but such effects were especially obvious at the 2.0 μg dose.

Effects of the *Sc. st.* Extract alone or in Combination with i.c.v. Injections of Muscimol or Bicuculline on Anxiety Behavior. Figure 3 illustrates the effects of oral administration of effective doses of the *Sc. st.* extract or of vehicle consecutively for 12 days alone or in combination with i.c.v. injections of muscimol (1 μg/rat) or bicuculline (1 μg/rat) on anxiety-related behavior in the EPM test. In the $GABA_A$ agonist-treated groups, one-way ANOVA revealed that muscimol significantly increased the OAT and OAE at the *Sc. st*. extract dose of 160 mg/kg, indicating lower levels of anxiety-related behavior in the *Sc. st.*+muscimol group in comparison with the water+muscimol (OAT: $F_{(2, 21)} = 7.49$, $P < 0.005$, and OAE: $F_{(2, 21)} = 4.25$, $P < 0.03$) or water+saline (OAT: $F_{(3, 28)} = 21.43$, $P < 0.001$, and OAE: $F_{(3, 28)} = 12.08$, $P < 0.001$) control groups. Bicuculline i.c.v. injections noticeably decreased the OAT and, to a somewhat lesser extent, OAE, as compared with the control indices. In addition, in the $GABA_A$ antagonist-treated



F i g. 2. Effects of intracerebroventricular injections of the $GABA_A$ receptor agonist or antagonist on rat behavior in the elevated plus-maze test. Control rats were treated with saline (1 μl/rat, Contr.), different doses of muscimol (0.5, 0.75, and 1.0 μg/rat), or bicuculline (0.5, 1.0, and 2.0 μg/rat) 5 min before the EPM test. A-C) Open-arm time, % (A), open-arm entries, % (B), and locomotor activity (C). $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$, compared to the control group. Other designations are similar to those in Fig. 1.

Р и с. 2. Впливи внутрішньошлуночкових уведень агоніста та антагоніста $ГАМК_A$-рецепторів на поведінку щурів у піднятому лабіринті.

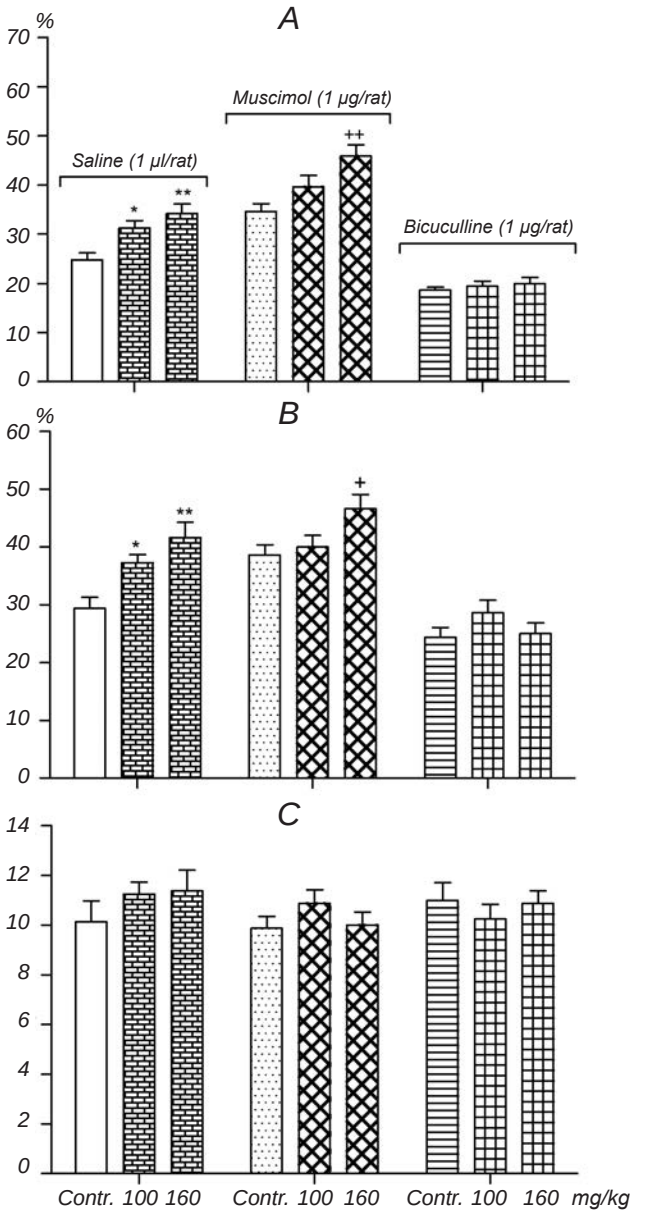
groups, one-way ANOVA revealed that bicuculline did not alter the OAT ($F_{(2, 21)} = 1.47$, $P > 0.05$) and OAE ($F_{(2, 21)} = 1.43$, $P > 0.05$) at all doses of *Sc. st.* in comparison with the water+muscimol control group. At the same time, bicuculline significantly decreased the former index, OAT ($F_{(3, 28)} = 5.96$, $P < 0.004$) and, somewhat but insignificantly, OAE ($F_{(3, 28)} = 1.71$, $P > 0.05$) at all doses of *Sc. st.* in comparison with the water+saline control group. No significant changes were observed in the LMA in all groups. Thus, bicuculline nearly completely eliminated anxiety-suppressing effects of the *Sc. st.* extract in the EPM test.

Two-way analyses revealed that there were no significant interactions between most effective doses of *Sc. st.* (Factor A) and muscimol (Factor B) on the OAT [Factor A: $F_{(2, 42)} = 15.17$, $P < 0.001$; Factor B: $F_{(1, 42)} = 42.62$, $P < 0.001$, and Factor (A × B): $F_{(2, 42)} = 0.4$, $P > 0.05$], OAE [Factor A: $F_{(2, 42)} = 11.99$, $P < 0.001$, Factor B: $F_{(1, 42)} = 11.24$, $P < 0.003$, and Factor (A × B): $F_{(2, 42)} = 1.27$, $P > 0.05$], and LMA [Factor A: $F_{(2, 42)} = 1.39$, $P > 0.05$, Factor B: $F_{(1, 42)} = 1.6$, $P > 0.05$, and Factor (A × B): $F_{(2, 42)} = 0.45$, $P > 0.05$].

However, two-way analyses revealed that significant interactions were observed between most effective doses of *Sc. st.* (Factor A) and bicuculline (Factor B) on the OAT [Factor A: $F_{(2, 42)} = 7.92$, $P < 0.002$, Factor B: $F_{(1, 42)} = 90.63$, $P < 0.001$, and Factor (A × B): $F_{(2, 42)} = 4.48$, $P < 0.02$] and OAE [Factor A: $F_{(2, 42)} = 6.58$, $P < 0.004$, Factor B: $F_{(1, 42)} = 38.44$, $P < 0.001$, and Factor (A × B): $F_{(2, 42)} = 4.45$, $P < 0.02$]. No significant interaction was found with respect to LMA [Factor A: $F_{(2, 42)} = 0.35$, $P > 0.05$, Factor B: $F_{(1, 42)} = 0.14$, $P > 0.05$, and Factor (A × B): $F_{(2, 42)} = 0.37$, $P > 0.05$].

Effects of the *Sc. st.* Extract on Depression Behavior in the FST. Figure 4A shows the effects of oral administration of different doses of the *Sc. st.* extract or vehicle consecutively for 12 days. One-way ANOVA and *post hoc* analysis revealed that the effects of *Sc. st.* were significant at the doses of 100 and 160 mg/kg. This extract decreased the total duration of immobility segments ($F_{(5, 42)} = 5.73$, $P < 0.001$). The results indicate that some antidepressant-like effects are observed following administration of the *Sc. st.* extract.

Effects of i.c.v. Injections of the $GABA_A$ Receptor Agonist and Antagonist on Depression Behavior. Figure 4B (left part of the panel) illustrates the effects of i.c.v. injections of different doses of muscimol. One-way ANOVA and *post hoc* analysis revealed that



F i g. 3. Effects of an extract from *Scrophularia striata* (*Sc. st.*) alone or in combination with intracerebroventricular (i.c.v.) injections of muscimol or bicuculline on anxiety behavior of rats in the elevated plus-maze test. Animals were treated with oral administration of the effective doses of the *Sc. st.* extract or vehicle consecutively for 12 days; then, the rats received i.c.v. injections of saline (1 µl/rat), muscimol (1 µg/rat), or bicuculline (1 µg/rat) 60 min after the last treatment with the extract and 5 min before testing. Each bar represents mean ± s.e.m. ($n = 8$) of open-arm time, % (A), open-arm entries, % (B), or locomotor activity (C). Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, compared to the control (Contr.) group; $^{+}P < 0.05$ and $^{++}P < 0.01$, compared to the water+muscimol control group.

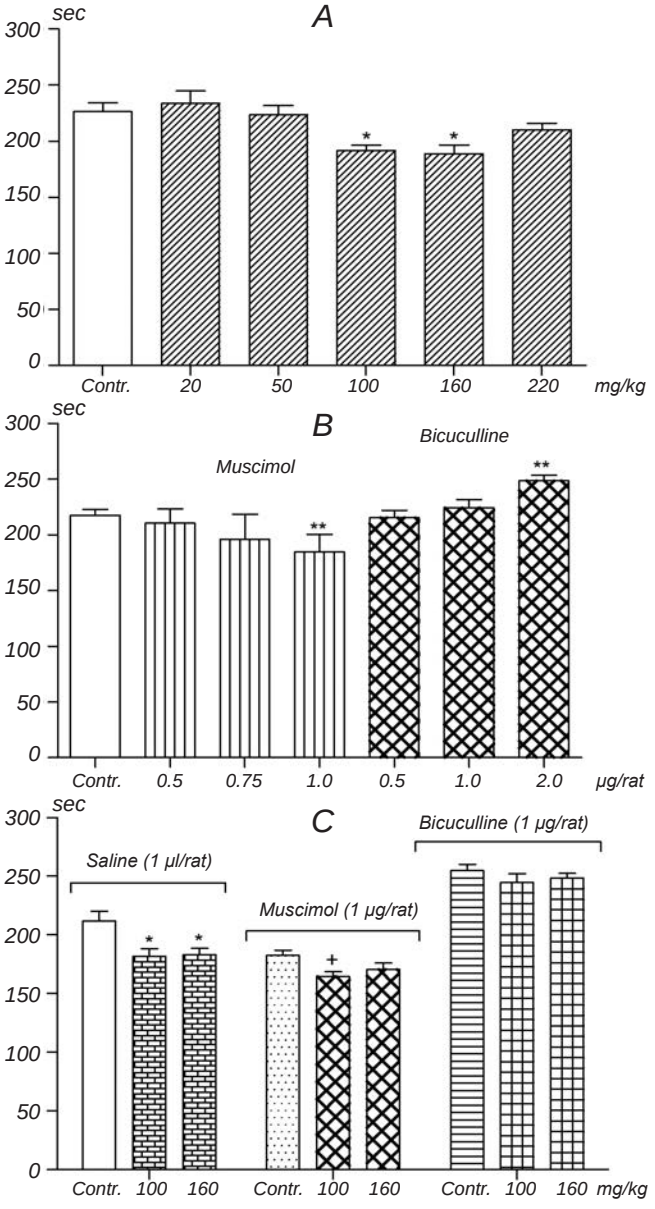
Р и с. 3. Впливи екстракту *Scrophularia striata*, введеного ізольовано або в комбінаціях із внутрішньошлуночковими ін'єкціями мусцимолу або бікукуліну, на показники тривожності щурів при тестуванні в піднятому лабіринті.

the effect of muscimol was significant at the dose of 1 μg/rat. Muscimol decreased the total duration of immobility ($F_{(3, 28)} = 5.92$, $P < 0.004$) in the FST. The data show that i.c.v. administration of the $GABA_A$ receptor agonist in sufficient doses exerts an antidepressive effect in the FST.

However, rats i.c.v. infused with different doses of bicuculline significantly increased the total duration of immobility periods ($F_{(3, 28)} = 6.04$, $P < 0.004$) at the dose of 2 μg/rat. These observations show that depression manifestations intensified in the FST following injection of the $GABA_A$ receptor antagonist (Fig. 4B, right part of the panel).

Figure 4C illustrates the effects of oral administration of effective doses of the *Sc. st.* extract or of vehicle consecutively for 12 days alone or in combination with i.c.v. injections of muscimol (1 μg/rat) or bicuculline (1 μg/rat) on the depression-related parameter in the FST. In the $GABA_A$ agonist-treated groups, one-way ANOVA revealed that muscimol significantly decreased the total duration of immobility at the *Sc. st.* dose of 100 mg/kg. Lower levels of depression in the *Sc. st.*+muscimol group in comparison with the water+muscimol ($F_{(2, 21)} = 3.68$, $P < 0.04$) or water+saline ($F_{(3, 28)} = 12.48$, $P < 0.001$) control groups were observed. In addition, in the $GABA_A$ antagonist-treated groups, one-way ANOVA revealed that bicuculline did not alter the total duration of immobility ($F_{(2, 21)} = 0.75$, $P > 0.05$) at all doses of *Sc. st.* in comparison with the water+muscimol control group but significantly increased the total duration of immobility ($F_{(3, 28)} = 8.30$, $P < 0.001$) at all doses of the extract in comparison with the water+saline control group. Again, no significant change was observed in the LMA index.

Two-way analyses revealed that there were no significant interactions between most effective doses of *Sc. st.* (Factor A) and muscimol (Factor B) on the total duration of immobility [Factor A: $F_{(2, 42)} = 9.1$, $P < 0.002$, Factor B: $F_{(1, 42)} = 15.43$, $P < 0.001$, and Factor (A × B): $F_{(2, 42)} = 1.05$, $P > 0.05$]. These analyses also revealed that there were no significant interactions between most effective doses of *Sc. st.* (Factor A) and bicuculline (Factor B) on this parameter [Factor A: $F_{(2, 42)} = 5.65$, $P < 0.008$, Factor B: $F_{(1, 42)} = 114.21$, $P < 0.001$ and Factor (A × B): $F_{(2, 42)} = 0.17$, $P > 0.05$] in the FST test.



F i g. 4. Effects of an extract from *Scrophularia striata* (*Sc. st.*) alone or in combination with intracerebroventricular (i.c.v.) injections of muscimol or bicuculline on depression behavior in the forced swimming test. A) Oral administration of different doses of the *S. s.* extract or vehicle consecutively for 12 days, B) i.c.v. injections of the $GABA_A$ receptor agonist or antagonist, and C) oral administration of the *Sc. st.* extract alone or in combination with i.c.v. injections of muscimol or bicuculline. Results of statistical analysis and *post-hoc* comparisons are described in Results. Each bar represents mean ± s.e.m. ($n = 8$) of total duration of immobility. Significant differences: $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, compared to the control (Contr.) or saline group; $^+P < 0.05$, compared to the water+muscimol control group.

Р и с. 4. Впливи екстракту *Scrophularia striata*, введеного ізольовано або в комбінаціях із внутрішньошлуночковими ін'єкціями мусцимолу або бікукуліну, на показники депресивності щурів у тестах вимушеного плавання.

DISCUSSION

To our knowledge, this is the first report on pharmacological effects of *Sc. st.* on neuropsychiatric indices in experimental animals. Our results demonstrated that administration of the *Sc. st.* extract decreases the levels of anxiety and depression-like behaviors in rats. As was mentioned above, a recently published study conducted by Monsef-Esfahani et al. [12] showed the presence of a quercetin flavonoid among effective compounds of this plant. On the other hand, some authors reported that quercetin can decrease the anxiety and depression levels [13, 14] and also demonstrated a relationship between the quercetin effects and the activity of neurotransmitter systems in the CNS [19-21]. Thus, mental-related behaviors can be altered through indirect mechanisms. To explore this issue further, we investigated the interaction between the effects of *Sc. st.* and the GABA-ergic cerebral system. In this regard, i.c.v. microinjections of muscimol decreased the levels of anxiety and depression, whereas administration of bicuculline in this brain site increased the levels of the respective disorders. The exact role of GABA-ergic networks in various areas of brain in the regulation of anxiety and depression has not been clearly recognized. Our data agree with the results of previous studies, which demonstrated that the GABA-ergic system plays an important role in the regulation and control of anxiety and depression, and that GABA-ergic agents or drugs exert powerful anxiolytic and antidepressive effects in humans and animals [9]. Moreover, another part of our study showed that co-administration of bicuculline with the *Sc. st.* extract decreased anxiolytic and antidepressant-like effects, while co-administration of muscimol with this extract increased the respective effects relative to the control group. These findings demonstrate that the $GABA_A$ agonist can enhance anxiolytic and antidepressive influences of active components of *Sc. st.*, while the $GABA_A$ antagonist considerably blocks these effects.

Furthermore, it is well known that stress activates the hypothalamic-pituitary-adrenal (HPA) axis mostly via stimulation of corticotrophin-releasing factor (CRF) release from the hypothalamus. In the next step, CRF stimulates secretion of adrenocorticotropin (ACTH) from the anterior pituitary and also that of the stress hormones, such as cortisol in humans and corticosterone in rodents [13]. As a consequence, it should be emphasized that the CRF system is responsible for the regulation of anxiety and depression-related behaviors. In line with this, a recent report demonstrated that quercetin attenuates stress-induced behavioral effects. It also decreases CRF expression in the brain [13]. On the one hand, numerous recent studies described anti-inflammatory effects of the *Sc. st.* extract in rodents, and the presence of quercetin flavonoid in this plant was identified [10, 12]. On the other hand, several studies demonstrated antioxidant, anti-inflammatory, neuroprotective, anxiolytic, and antidepressive effects of quercetin in experimental models [13, 14]. Collectively, it is conceivable in the light of presented evidence that the effects of *Sc. st.* could be mostly related to the presence of quercetin among the constituents of this plant.

Therefore, our experiments showed that the extract of *Sc. st.* effectively decreases the levels of anxiety and depression in rats. Although the mechanisms providing suppression of these disorders under the conditions tested are likely complex, the above evidences suggest that the GABA-ergic system may mediate, to a conciderable extent, the effects of the *Sc. st.* extract. More studies are needed to investigate more fully these pharmacological effects and the respective involvement of different neurotransmitter systems.

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УЧАСТЬ ГАМК-ЕРГІЧНОЇ СИСТЕМИ В АНКСІОЛІТИЧНИХ ТА АНТИДЕПРЕСИВНИХ ЕФЕКТАХ ЕКСТРАКТУ *SCROPHULARIA STRIATA* У ЩУРІВ

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Нещодавно в експериментах на гризунах були продемонстровані нейропротективні та протизапальні ефекти екстракту ранника смугастого, *Scrophularia striata* Boiss (*Sc. st.*, *Scrophulariaceae*). Ми досліджували впливи екстракту *Sc. st.* на аспекти поведінки щурів, пов'язані з тривожністю та депресивністю, і намагалися з'ясувати механізми, відповідальні за реалізацію цих впливів. Тестували поведінку в піднятому лабіринті (ПЛ) і в тесті вимушеного плавання (ТВП). 20, 50, 100, 160 або 220 мг/кг сухої речовини спиртового екстракту *Sc. st.* уводилися перорально у вигляді вод-

ного розчину. Ми також досліджували взаємодію екстракту *Sc. st.* в ефективних дозах і $ГАМК_A$-рецепторів у головному мозку. Екстракт у дозах 100 та 160 мг/кг забезпечував вірогідне збільшення нормованих значень часу перебування у відкритій гілці ПЛ і числа входів до неї і зменшував тривалість періоду нерухомості в ТВП порівняно з відповідними значеннями в контрольній групі; це свідчило, відповідно, про анксіолітичний та антидепресивний ефекти. Внутрішньошлуночкові введення агоніста $ГАМК_A$-рецепторів мусцимолу (0.5, 0.75 і 1 мкг на тварину) посилювали відповідні ефекти *Sc. st.* Антагоніст же $ГАМК_A$-рецепторів бікукулін (0.5, 1 і 2 мкг на щура) блокував ці ефекти. Таким чином, анксіолітичні та антидепресивні ефекти активних компонентів *Sc. st.* можуть опосередковуватися модуляцією стану ГАМК-ергічної системи.

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