To the pharmacology of "St. John's herb" (Hypericum perforatum - Hypericum perforatum). First message

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Pharmacological properties of St. John's wort (Hypericum perforatum). The first report

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SUMMARY

Summarizing the information on the use of the aerial part of St. John's wort in a number of diseases and syndromes of a neurological profile, as well as in epilepsy, the effect of its infusion, the flavonoids of hyperoside, quercetin, kaempferol, rutin isolated from it, the amount of flavonoids on convulsions caused by corazole, strychnine, thiosomalis and maximum electric shock (MES). Having established the absence of anticonvulsant properties of phytopreparations in comparison with the once injected classical anticonvulsants seduxen and depakin, a moderate increase in tolerance to corazole, thiosemicarbazide and MES was recorded against the background of a course, but not a single dose of St. John's wort infusion. The generally accepted method of recording the loss of the conditioned passive avoidance reflex after MES was used to study the ability of phytopreparations to prevent amnesia of this reflex. Only an infusion of St. John's wort was effective in course of enteral administration. The experiments were carried out on male SHR mice. It was concluded that the use of St. John's wort infusion for convulsive syndromes is based not on its anticonvulsant, but on its cerebroprotective properties, which are manifested in the ability to prevent damage to the basic, reflex forms of animal behavior that ensure the survival of the individual and the species. The data obtained are consistent with the results of our experimental studies of the pharmacological properties of medicinal plants used for epilepsy and other neuropsychiatric diseases, in which cerebroprotective but not anticonvulsant activity is registered in simple galenic forms. Both types of activity were not found in flavonoids, terpenoids, coumarins, phenolcarboxylic,

Keywords: phytopharmacology, St. John's wort perforated, cerebroprotective activity.

RESUME

Data on the use of the aerial parts of Hypericum for treatment of diseases and syndromes of neurological profile as well as epilepsy was summarized. We investigated the effect of Hypericum perforatum infusion and isolated hyperoside flavonoids, quercetin, kaempferol, rutin, total flavonoids on convulsions caused by corazol, strychnine, thiosemicarbazide and maximal electroshock (MES). We did not establish of anticonvulsant properties of herbal remedies single use compared to a single injection of

classical anticonvulsants Seduxenum and depakine, and registered a moderate increase in tolerance to corazol, thiosemicarbazide and MES after Hypericum therapy course. Using generally accepted method of recording the loss of passive avoidance after MES we studied the ability of herbal remedies to prevent amnesia of this reflex. Only course enteral administration of St. John's wort infusion was effective. Experiments were carried out on SHR male mices. It is concluded that the use of St. John's wort tincture for treatment of seizures is not based on anticonvulsant, but on cerebroprotective properties manifested in the ability to prevent damage to the base, reflex behaviors of animals to ensure the survival of the individual and the species.

These findings are consistent with the results of our experimental study of the pharmacological properties of medicinal plants used in epilepsy and other neuropsychiatric diseases which have shown that simple galenic forms have cerebroprotective but not anticonvulsant activity.

Both types of activity were not detected in flavonoids, terpenoids, coumarins, phenolcarboxylic and other organic acids and other natural forms isolated from these plants.

Keywords: phytopharmacology, Hypericum perforatum, cerebroprotective activity.

Introduction

The names of many highly effective medicinal plants are associated with ideas about the healing power given to them by God, higher powers: God's tree (Healing wormwood), Bogorodskaya herb, incense (creeping thyme), Angelika or Archangelika (Angelica species), Sacred Prutnyak or Abraham's tree or Vitex innocent lamb, Artemis herb (Common wormwood), Symbol of the Passion of Christ (Passion flower incarnate), gift of the Virgin Mary (Milk thistle), sacred herb (Hyssop medicinal - from Hebrew esso), divine flower or flower of Zeus (Fischer's Carnation), Moses bush (blackthorn, prickly plum), St. John's herb (the name of St. John's wort in English-speaking countries) [1,2]. The name St. John's wort itself comes from the distorted Kazakh "djerbay" - a healer of wounds. These plants, indications for their use, deserve special attention,

In many sources, St. John's wort is considered indicated not only for diseases of the gastrointestinal tract and hepatobiliary system, for wounds and injuries, but also for a number of diseases and syndromes of a neurological profile: neurasthenia, hysteria, depression, phobias, neuralgia, sciatica, cephalalgia, sleep disturbances , nocturnal enuresis [1, 3, 4, 5], with convulsions, epilepsy [6]. Highly appreciating the therapeutic value of St. John's wort, M.A. Nosal and I.M. Nosal [7] by no means exaggerated it: “This is the most important plant we all know. People call it "the herb for ninety-nine diseases." Just as bread cannot be baked without flour, so many diseases of people and animals cannot be cured without hypericum. " The established reputation of St. John's wort as a tonic, anti-asthenic, moderate tonic (non-stimulant),

multicomponent personified collection of patients with various neurological diseases [8] determined the purpose of the research: to experimentally study the anticonvulsant properties of its infusion in comparison with flavonoids isolated from it and the effect of these phytopreparations on the loss of the conditioned passive avoidance reflex (passive avoidance reflex).

Materials and research methods

The aboveground part of St. John's wort was collected during the flowering period in the floodplain of the river. Oyat Podporozhsky district of the Leningrad region. An infusion of 1:10 was prepared according to the State Pharmacopoeia ex tempore on the day of enteral administration via a tube (0.5 ml / 10 g or 5 g / kg in terms of air dry raw materials) to 20–25 g SHR male mice. Spectrographically pure flavonoids were provided by Cand. chem. Kozhina I.S. and other employees of the phytochemistry group of the Botanical Institute. V.L. Komarov RAS. Flavonoids (hyperoside, rutin, quercetin, kaempferol, the sum of St. John's wort flavonoids) were emulsified in 10% Tween-80 emulsion, the same amount of emulsifier was used in the control, and was also added to the St. John's wort infusion to equalize the experimental conditions. Emulsions of flavonoids and their amounts were also injected into the stomach in single doses of 10, 50, 100 mg / kg for 7 days. Wrongfulness of injection,

When comparing the anticonvulsant properties of the drugs, we used the generally accepted method of “titration” of DL100 corazole with slow (0.1 ml / 20 sec.) Introduction of a 0.5% solution into the tail vein of the mouse before the onset of seizures [10]. Complete protection is considered the absence of seizures after injection of 1 ml for 3 minutes. 20 sec. (250 mg / kg corazole). The method of maximum electroshock (MES) [11] was used in a modification developed by us with the use of oral electrodes [9], guaranteeing seizures in all control mice and making it possible to more than halve the current parameters to 20–30 mA (50 Hz, 0.1 sec.). In the experiments, the number of mice without seizures was counted, since oral electrodes can almost completely prevent mortality. Thiosemicarbazide, a GABA synthesis blocker, was injected into mice intravenously at a dose of 17 mg / kg,

The generally accepted method of loss of the conditioned passive avoidance reflex (CPAR) after MES was used to compare the cerebroprotective properties of phytopreparations. This method was the first to reveal the cerebroprotective properties of Eleutherococcus preparations [12]. The mice were placed on a brightly lit area, to which they immediately preferred a shaded area, where they received painful stimulation of the legs with electric current. After that, the animals no longer visited the shaded area, avoiding the premises that were dangerous for them. This passive avoidance reaction is generated at one time and is saved on the following days. In most experiments, all animals of the control group lose CPAR after MES, without demonstrating it on

the next day. The number of mice that did not lose passive avoidance reaction after MES were counted against the background of the studied drugs. The results were processed statistically according to the χ^2, t criteria and were considered reliable in cases of differences with the control at $p \leq 0.05$. Mean values ± confidence interval are given in the text.

results

When “titrating” the DL100 of corazole in the control, it was equal to 58.0 ± 8.0 mg / kg (100 ± 13.7%). After 7 days of enteral administration of St. John's wort, it significantly increased to 71.9 ± 7.2 mg / kg (124 ± 12%). Due to the ineffectiveness of flavonoids and their sums in the given doses, both with a single dose and with a course administration, we omit the digital material. The results for the course administration of St. John's wort infusion have been reproduced many times. For example, when the infusion was administered enterally without an emulsifier at the same dose for 7 days, DL100 of corazole significantly increased from 87.0 ± 8.0 to 99.0 ± 6.5 mg / kg (from 100 ± 9.2 to 114 ± 7.5%). A single introduction of the infusion before the "titration" of DL100 corazole did not lead to its decrease, which indicates the need for course administration of it. At the same time, a single enteral administration of seduxene (5 mg / kg) or depakine (20 mg / kg) completely protected the mice from seizures and death. In experiments with strychnine, none of the studied drugs was effective. The drugs did not prevent the convulsive effect of thiosemicarbazide, unlike seduxen, but the infusion of St. min. The sum of flavonoids of the aerial part of St. John's wort at a dose of 100 mg / kg extended only the latent period of seizures to 50 ± 6 minutes. The results of experiments with thiosemicarbazide are less reproducible due to significant fluctuations in control parameters. In general, for the infusion of St. John's wort, they were confirmed in 2 out of 3 experiments, and for the sum of flavonoids in 1 out of 3, which allows registering an increase in animal tolerance to thiosemicarbazide against the background of infusion. Seduxen at a dose of 5 mg / kg once enterally completely prevented convulsions caused by thiosemicarbazide, and therefore the anticonvulsant activity of phytopreparations can be rejected.

Table 1 shows the results of studying the effect of St. John's wort preparations on seizures caused by MES and their ability to maintain CPAR. The limitation of seizures consisted in the absence of tonic contractions, but short-term (several seconds) elements of clonus were observed in all mice, so that, strictly speaking, this effect cannot be called anticonvulsant, since seduxen at doses of 5-10 mg / kg once enterally demonstrated complete protection in 7 and 10 out of 10 animals, respectively. As follows from the table. 1, the absence of tonic convulsions against the background of the infusion of St. John's wort was not a guarantee of the preservation of CPAR, just as their presence did not lead to its loss. The lack of correlation between anticonvulsant and antiamnestic properties of drugs is well known. Even animals without tonic seizures underwent the damaging effects of the MES, which manifested itself in complete weakness after an electrical injury. Due to the reliable efficiency of the St. John's wort infusion, the experiments with the preparation of animals for the MES were reproduced. The preservation of CPAR after MES was recorded in 7, 8, and 10 mice out of 20 in subsequent experiments. In the latter case, the test was carried out on females, confirming that the manifestation of cerebroprotective

properties does not depend on the sex of the animals. A single or even double administration of a 1:10 infusion of St. John's wort in a maximum dose (5–10 g / kg in terms of air-dry raw materials, respectively) only on the day of the experiment did not lead to protection against tonic convulsions and loss of passive avoidance reaction, which is consistent with the theory of state nonspecifically increased resistance of the organism caused by classical adaptogens [9, 12] and a number of other plants, but not achieved with a single administration of their preparations [8, 9].

The discussion of the results

Some neglect of simple galenic forms, an emphasis on the isolation of "active" substances, carriers of the effect leads to serious mistakes in the strategy and tactics of finding effective means of improving people. For centuries, millennia in folk and traditional medicine in the presence of many dosage forms ("St. John's wort oil", plant powder, tincture, ie vodka infused with St. John's wort), infusion, or rather tea, dominated and dominates. It is water that has been and remains the main extractant in the systems of traditional medicine in Asian countries. The tradition of preventive consumption of herbal teas (tavozhny, linden, Kuril, Kaporsky, Kalmyk, blackberry and other teas) is dying out and only a few specialists know about many of these teas, especially about the possibilities of their general strengthening effect. St. John's wort has always been considered a surrogate for tea, which was drunk not only for medicinal, but also for prophylactic purposes. Its popularity on different continents is an indirect confirmation of its high efficiency. However, even in screening tests, its effect on damaging effects in relation to the functions of the central nervous system has not been studied, sometimes it has been studied eclectically or not systematized.

Table 1

Comparative assessment of the anticonvulsant activity of St. John's wort preparations at maximum electroshock (MES) and their effect on preservation conditioned passive avoidance reflex (passive avoidance reflex)

Препарат, доза	количество мышей		
	в группе	без тонических судорог	не утративших УРПИ после МЭШ
Настой травы зверобоя 1:10 – 0,5 мл/10 г (5 г/кг)	20	11*	15*
Сумма флавоноидов 100 мг/кг	20	5*	4
Кверцетин 100 мг/кг	20	3	2
Гиперозид 100 мг/кг	20	2	0
Кемпферол 100 мг/кг	20	2	0
Рутин 100 мг/кг	20	2	1
Контроль 10 %-ная эмульсия Tween-80	30	0	0

Примечания: 1) звездочкой обозначены результаты, достоверно отличающиеся от контроля по непараметрическому критерию χ^2 при $p \leq 0,05-0,01$; 2) меньшие дозы флавоноидов опущены в связи с отсутствием эффекта.

Having set the task of studying the effect of St. John's wort preparations on convulsive

deadly action four standard used by at search anticonvulsants of convulsive agents (corazole, strychnine, thiosemicarbazide) and effects (MES), wanted to assess the motivation for using it in convulsive forms of epilepsy. The results obtained do not allow us to classify St. John's wort as anticonvulsants, in particular the herb infusion, which showed some minimal activity in the tests with MES, corazole and even less in the test with thiosemicarbazide. The classical anticonvulsants anticholinergic depakin and the NMDA receptor blocker seduxen completely protected animals in three of the four models of seizures we used with a single injection, which was not observed for any of the studied phytopreparations. The decrease in DL100 of corazole against the background of a 7-day infusion of the infusion is most correctly regarded as an increase in the resistance of animals to the toxic effect of the convulsant. The very moderate activity of the infusion under the influence of MES and thiosemicarbazide can be interpreted in the same way. The seizure component itself was not completely arrested with MES (single clones), and even more so with the injection of thiosemicarbazide. The ineffectiveness of flavonoids and the moderate detoxification activity of their amount, which has no practical significance, should be taken into account when critically assessing the clinical significance of a number of St. John's wort drugs (Hyperforin, Floristen, Peflavit, Deprim, Life 600, Prostanorm ...) connections it. However, the abundance of drugs from St. John's wort is another evidence of the popularity, effectiveness of this plant and attempts to isolate antidepressants, anticonvulsants from it, comparable in activity to synthetic drugs.

Our results of nonspecific increase in confirm significance theory resistance organism. Having experience experimental evaluation of the absence of anticonvulsant properties of galenic drugs, a number of natural compounds from plants used in traditional medicine for epilepsy [8, 9], supported by the above results, it can be assumed with sufficient guarantee that the herbal medicine of epilepsy patients in folk and traditional medicine was not based on their lack of anticonvulsant action, the ability to eliminate the symptom, and on some other, more essential properties. Hypothetically, one can assume their ability to correct metabolism, the balance of endogenous convulsants and anticonvulsants [13], which cannot be achieved with a single dose of the drug. It is the correction of the balance of mediators, peptides, neuroactive acids, energetically active substances (assessment is practically impossible) should be suspected as one of the main mechanisms of the cerebroprotective effect of plants. An eclectic study of any one link does not provide confidence in the clinical significance of the result. Therefore, the importance of detecting these cerebroprotective properties by methods of establishing the ability of plants to preserve and preserve the main, basic forms of animal behavior is increasing.

One of these methods used in testing the nootropic properties of drugs is the method of preserving CPAR after MES. Interpretation of the results,

given in table. 1 is not difficult. Only the infusion of St. John's wort allowed the animals to preserve the CPAR, which was subsequently reproduced. The experience of testing the cerebroprotective properties of phytopreparations by various methods made it possible to note earlier that none of the many tens of natural compounds from the class of flavonoids, terpenoids, coumarins, phenolcarboxylic acids, azulenes possesses these properties, in contrast to the total aqueous and alcoholic extracts. These results are consistent with those obtained in this study. It is obvious that the development and implementation of reflexes of passive and active avoidance underlies the survival of the individual and the preservation of the species. Understanding, studying the positive influence of plants on the preservation of basic forms of animal behavior, their role in maintaining the constancy of biogeocenosis, in the reproduction of representatives of the fauna is one of the most promising directions in the search for effective methods for the prevention and treatment of diseases of the nervous profile and others with the help of medicinal plants and their combinations. Practical confirmation of the correctness of this approach to phytotherapy methods, based on knowledge and consideration of biological laws, is given by us in the monograph "Phytotherapy in Neurology" [8].

conclusions

1. The use of the aerial part of St. John's wort in epilepsy and a number of others diseases of the neurological profile is not based on the lack of anticonvulsant properties. Unlike classical anticonvulsants, St. John's wort preparations are ineffective with a single administration. With the course administration, the infusion of St. John's wort also did not completely protect the animals from seizures, but increased the tolerance to corazole, electrical injury, thiosemicarbazide. The flavonoids of St. John's wort were ineffective, the insignificant effectiveness of their sum has no practical significance.

2. Preservation of the conditioned reflex of passive avoidance after the maximum electroshock was provided only by the infusion of St. John's wort, which indicates the presence of cerebroprotective properties.

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