THE PHARMACOLOGY OF THALICARPINE

I — The Influence of Thalicarpine and Some of Its Quaternary Salts upon Striated Muscle Contractions

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Recently, a new alkaloid group was discovered with hitherto unknown aporphine-benzyl-isoquinoline structure (13, 14). Kupchan, M. and assoc. isolated its first representative, called Thalicarpine, from the roots of Thalictrum dasycarpum and established its structure (13), whereas Mallov and Duchevska (14) obtained it from the overground parts of the widespread in Bulgaria plant Thalictrum minus ssp. elatum. Tomimatsu T., E. Vorperian, J. L. Beal and M. P. Cava (16) derived it from the plant Thalictrum revolutum. Lately, the original structure of this alkaloid, described by Kupchan and assoc., was corrected insofar location of the oxygen bridge is concerned, by a team of workers in which Kupchan too participated (13a). As a result of all these studies, presently the structure of the thalicarpine assumes the appearance illustrated in figure 1.

In accordance with pharmacological investigations already published, the thalicarpine accounts for a reduction of blood pressure due to the bradycardia, respiratory depression and slight adrenalysis produced. In larger doses per os, it causes a weak antidiuretic effect, slightly attenuates the pain and brings about an insignificant decrease of body temperature, but is devoid of anticoagulation, hyperglycemic and anticonvulsive action (13).

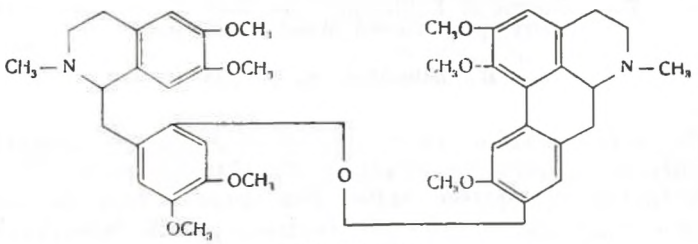
Heretofore, we have not come across data concerning the influence of thalicarpine as well as of other thalictrum alkaloids, upon the function of striated musculature (1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). Indeed, Drumev (2) claims of having investigated the active principles of thalictrum for eventual curare-like action, but unfortunately, his information proving the absence of influence in this respect is unacceptable on account of several reasons. First and foremost, he worked with alcohol-water extracts, and not with alkaloids, thalicarpine the least; secondly, thy type of thalictrum he employed is unknown and thirdly, as it will be seen later, our results, are contradictory in character.

We decided to pay particular attention to the action exerted by thalicarpine upon striated muscles and to study it separately by virtue of the fact that in the course of the analysis of the pharmacological properties of alkaloids, derived from various kinds Thalictrum, we came across data which, in our opinion, assume a definite interest from different viewpoints.

Thus, objective of the present report are the early results of investigations upon the influence of thalicarpine and some of its quaternary salts exerted upon striated muscles.

Material and Method

Besides to thalicarpine, we also studied five of its quaternary salts, namely: with methyl bromide, with ethyl iodide, with propyl iodide, with butyl iodide and ethyl acetate-iodide*. At the present stage of the work, all six compounds were investigated chiefly as regards contractions of striated muscles. In the great majority of experiments their effect upon the blood pressure was also tested.



Thalicarpine

The experiments were carried out on 65 cats of both sexes, weighing between 2 and 5 kg, under urethan anesthesia. Recordings were made of the m. gastrocnemius contractions during stimulation of the peripheric end of the cut ipsilateral sciatic nerve. Stimulation of the nerve was accomplished with the aid of rectilinear impulses of a frequency 0.1—0.2 Hz, duration 5 m/sec and amplitude 0.2—2 V, generated by an electron stimulator. The blood pressure was registered after the blood method suggested by Zyon-Ludwig in the cannulated left femoral artery.

Thalicarpine was administered intravenously in doses 0.5, 1.2 and 3 mg/kg weight, whereas its salts — in quantities equimolecular to the latter doses. Various doses, accordingly described, were also utilized in single experiments.

Results

Experiments with thalicarpine: (12 animals). In a dose of 0.5 mg/kg weight, the thalicarpine did not influence muscle contractions, whereas the blood pressure was temporarily reduced. It brought about intensification of muscle contractions in 5 out of a total of 7 animals when administered in doses amounting to 1 mg/kg weight (Fig. 1). This effect occurred at average 27 minutes after the introduction of the alkaloid and was manifested in varying degrees, persisting for different length of time, from 30 min to 2 and more hours (Table 1). In the experiments with 3 and 5 mg/kg weight changes in the contractions of m. gastrocnemius (Table 1) were not recorded.

Experiment with thalicarpine-methyl-bromide (4 animals): In none of the experiments carried out on 4 cats did we succeed recording changes in muscle contractions.

* The thalicarpine salts listed and the thalicarpine itself as well were kindly put at our disposal by Haymova and N. Mollov, enabling us to carry out the present investigations. On this account we would like to express them our deepest gratitude.

Table I

Substance	Dose in mg number of experiments	Number of experiments with + effect	% of experiments with + effect	Speed of effect occurrence after average	Increase of muscle contractions in % as to initial values
1	2	3	4	5	6
Thalicarpine hydrobromide (12)	0.50 (1) 1.00 (7) 3.00 (3) 5.00 (1)	— 5 — —	71	27 min	+ 145
Thalicarpine methylbromide (4)	0.60 (1) 1.25 (1) 3.64 (2)	— — —			
Thalicarpine ethyliodide (27)	0.68 (1) 1.36 (5) 2.60 (3) 3.00 (10) 4.00 (8)	1 1 1 8 3	 20 33 80 57	50 sec 40 sec 40 sec 25 sec 75 sec	+ 40 + 30 + 40 + 80 + 28
Thalicarpine propyliodide (4)	0.69 (1) 1.40 (1) 3.00 (1) 4.20 (1)	— 1 — —	?	20 sec	?
Thalicarpine butyliodide (14)	0.70 (1) 1.40 (6) 2.10 (1) 3.00 (1) 4.20 (5)	1 6 1 — 4	 100 80	40 sec 29 sec 30 sec 26 sec	+ 30 + 47 + 25 + 40
Thalicarpine ethyl acetate iodide (4)	1.45 (3) 4.36 (1)				

Experiment with thalicarpine-ethyl iodide (27 animals): As illustrated in table 1, in 14 of the experiments the ethyliodide salt of the thalicarpine brought about intensification of muscle contractions. The 3 mg/kg weight dose proved relatively more efficient in this respect. In all positive experiments the effect occurred following a short latent period, equal to an average of 25 sec, and continued for variable periods of time — from 15 min to 2—3 hours (Fig. 2 ab). The blood pressure decrease was not much more strongly manifested than with the thalicarpine series.

Experiment with thalicarpine-propyl-iodide (4 animals): Few experiments were carried out with this thalicarpine salt owing to the fact that a sufficient quantity was unavailable. As illustrated in figure 3, merely in one instance did we succeed in establishing a very slight

relief of muscle contractions. The activity of this compound insofar blood pressure is concerned is stronger as compared to the original product — thalicarpine.

Experiments with thalicarpine-butyl-iodide (14 animals): Intensification of the contractions of m. gastrocnemius (Ta-

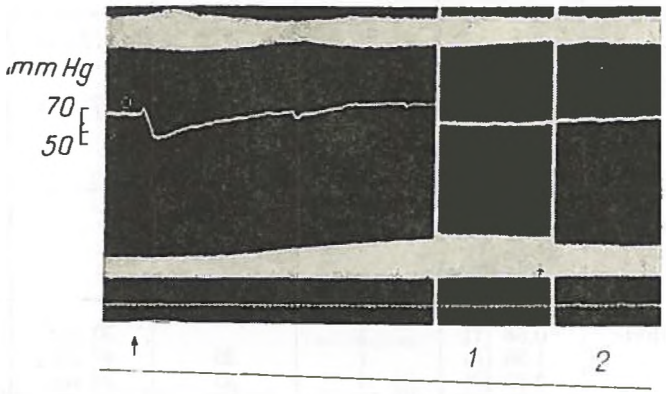


Fig. 1. The effect of talicarpine (T) hydrobromide on respiration, blood pressure and contractions of m. gastrocnemius

At ↑ — i. v. 1 mg per kilo body weight T. HBr., at 1—30, at 2—60 min after the administrationof T. HBr. From top to bottom: respiration, blood pressure, mechanokymogram of m. gastrocnemius contractions, recordings of time every 10 seconds

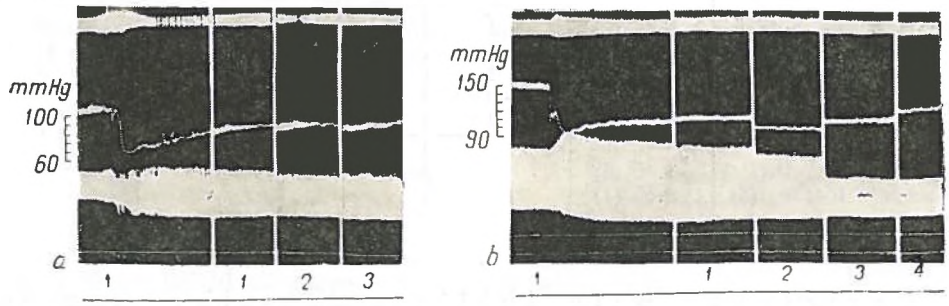


Fig. 2

a — the influence of T. C_2H_5I (at ↑ i. v. 1.3 mg/kg) on respiration, blood pressure and muscular reduction. At 1, 2, 3—30, 60 and 90 minutes after administration of the substance. b — identical, only i. v. 4 mg/kg T. C_2H_5I is administered at ↑. The order of recordings as in figure 2

ble 1) was obtained with all doses tested in 13 out of a total of 14 animals. The effect was variable in degree and duration, and compared to the effect of the ethyl salt, it was more feebly manifested (Fig. 4). Likewise the latter, it occurs promptly — average 30 sec after introduction of the substance.

As to the properties of this particular thalicarpine salt accounting for the reduction of blood pressure, no changes whatsoever were noticed as compared to the same property of thalicarpine.

Experiments with thalicarpine-ethyl-acetate iodide (4 animals). This quaternary salt of the thalicarpine is distinguished from the listed hitherto compounds mainly in two lines:

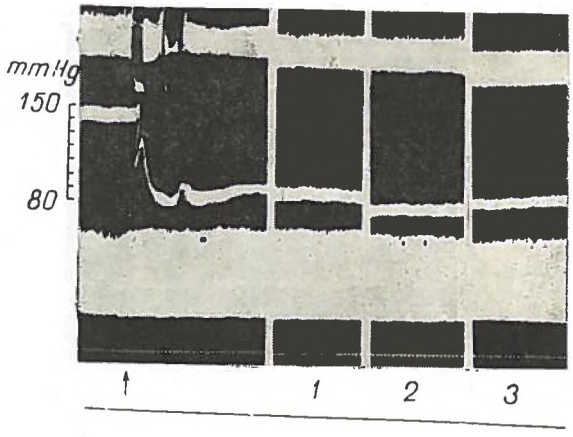


Fig. 3. The effect of T. C_3H_7I (at ↑ i. v. 1.4 mg/kg weight) on respiration, blood pressure and muscle contraction

At 1—30, at 2—60 and 3—90 min. after administration of the substance. Order of recordings asin figure 2

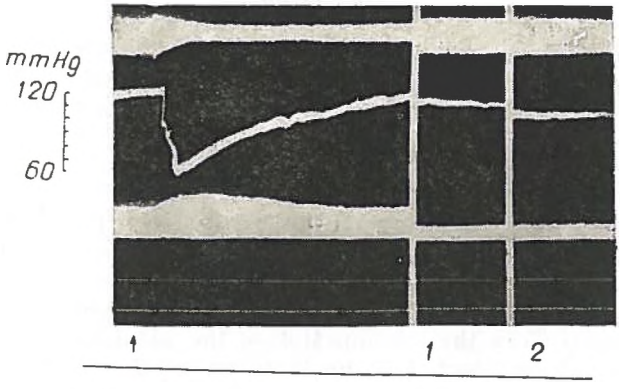


Fig. 4. Effect of T. C_4H_9I (at ↑ i. v. 1.4 mg/kg weight) on respiration, blood pressure and muscle contractions

At 1—30, at 2—60 min. after administration of the substance. Order of recordings as in figure 2

1) Instead of relieving, similarly to the latter, it inhibits up to full suppression the m. gastrocnemius contractions (Fig. 5) and 2) The blood pressure fall it causes is distinguished by its considerably longer duration (Fig. 4).

All six products investigated display a unidirectional influence upon respiration, manifesting itself in transitory excitation, occurring almost immediately upon administration. Subsequently, breathing returns to normal pattern.

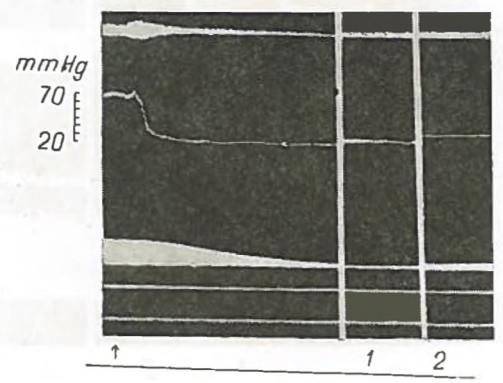


Fig. 5. The effect of T. $ICH_2COO.C_2H_5$ (at 4.4 mg per kg weight) on respiration blood pressure and muscle contractions
At 1-30, at 2—60 min. after administration of the substance. Order of recordings as in figure 2

Discussion

Leaving apart the experiments with the latter thalicarpine quaternary salt which impairs muscle contractions, as well as those with thalicarpine-methyl bromide and thalicarpine-propyl-iodide (2), which show no significant effect in the direction studied according to our personal up-to-date though limited experience, in 31 of the remainder 53 experiments, i. e. 58.5%, the thalicarpine and its quaternary salts with ethyl- and buthyl-iodide lead to an intensification of the m. gastrocnemius contractions in varying degrees. This effect of theirs varies considerably in duration. The difference between the thalicarpine action in this respect and the action of the ethyl- and butyl iodide salts of the same consists in the latent period; i. e. the time span since the introduction of the substance and the moment of manifestation of its effect. For the thalicarpine it is within range of minutes and considerably exceeds, insofar duration is concerned that of its derivatives. For the time being it appears difficult to explain the cause for this phenomenon. It is likewise difficult to assume a definite attitude concerning the lack of effect in the studied direction on behalf of methyl bromide and occasionally propyl iodide salt of the thalicarpine, i. e. the derivatives of the latter in which the quaternization of the nitrogen is accomplished through adjustment of an aliphatic chain with odd number of carbon atoms to it. These substances need further experimentation, firstly, to the end of verifying the reality of the findings described, and secondly — assessment of their importance.

The quaternization of the nitrogens of the thalicarpine with ethyl ester of the acetic acid is with negative sign, i. e. in this case too, the newly produced compound has preserved its myotropic nature, only now it is with negative sign. This alteration in the thalicarpine molecula brings about a strengthening of its hypotensive effect as well.

At the actual state of the research studies in course, we abstain of postulating a definite opinion on the question whether the substances studied exert a direct myotropic effect in positive or negative direction, or they alter in some manner the conditions of conducting the impulses into the myoneural synaptic relationships. Accumulation of additional informations is required for elucidating these and other questions; for this purpose new experimental projects are in course.

Inferences

The investigation on the effect of thalicarpine, derived from Thalictrum minus var. elatum, as wells on five quaternary salts of the latter upon striated muscles shows that:

1. The thalicarpine and its ethyl- and butyl-iodide salts in the majority of experiments (58.5%) stimulate in a great degree and for long duration the m. gastrocnemius contractions. Contrary to the effect of these salts, the effect of thalicarpine is manifested following a prolonged latent period.

2. The methyl-bromide and propyl-iodide quaternary salts of the alkaloid do not exert influence whatsoever upon muscle contractions, induced by electrical stimuli through indirect routes. However, the experiments with these thalicarpine derivatives are insufficient in number to warrant a definitive conclusion in this respect.

3. The ethyl-acetate-iodide is the only thalicarpine derivative accounting for the impairment to full inhibition of the m. gasctrocnemius contractions.

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ФАРМАКОЛОГИЯ ТАЛИКАРПИНА

I. Влияние таликарпина и некоторых его солей на сокращение поперечно-поласатой мускулатуры

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РЕЗЮМЕ

Авторы исследовали влияние таликарпина, изолированного из Thalictrum minus, ssp. elatum, и 5 его четвертичных солей на поперечно полосатую мускулатуру. Они находят, что, как таликарпин, так и его этиловые и бутил-йодная соли, в большинстве опытов стимулируют в значительной степени и длительное время сокращения m. gastrocnemius. В различие, однако, от эффекта солей, эффект таликарпина проявляется после значительно более длительного лятентного периода.

Метил-бромидная и пропил-йодидная соли таликарпина не оказывают влияния на индуцированные, при помощи электронных стимулов индиректным путем мышечные сокращения. Число опытов с этими таликарпиновыми производными недостаточно, чтобы можно было делать выводы.

Единственно этил-ацетат-йодидная соль таликарпина затрудняет до полного подавления сокращения m. gastrocnemius.

Полученные результаты подвергаются обсуждению.