Acta Biologica Szeged. *21* (1—4), pp. 113—125 (1975)

THE EFFECT OF TERTIARY TROPINE DERIVATIVES ON CEREBRAL CONVULSIONS

O. FEHÉR, G. A. BÁLINT and Á. BALOGH

Department of Animal Physiology, Attila József University, Szeged

(Received March 25, 1975)

Abstract

The anticonvulsive effects of tertiary tropine derivatives were studied on pharmacological and electrical seizures of anaesthetized cats and on electroshock of waking rats. Six out of twenty compounds examined, proved to be effective on these tests. The significant anticonvulsive potency of diphenyl-acetic and Xanthen-9-carbonic derivatives of tropine deserve special attention.

During our previous experiments (FEHÉR, HALÁSZ, MECHLER, 1965) it was shown that the atropine applied to the cortex abolished the rhythmic after-discharges produced by acetylcholine and eserine, but had no effect on the strychnine potentials. From this fact the conclusion was drawn that in the mechanism of the rhythmic after-discharge cholinergic synaphes may play a role; the acetylcholeni may have an excitatory effect, or perhaps due to an inhibitory action it may enhance the activity of excitatory circuits.

Starting from these results it was examined whether the teriary derivaties of tropine which did not contain tropic acid have any inhibitory effect on the rhythmic after-discharge produced by acetylcholine and eserine, or not?

Our experiments had two main purposes. First, the anticonvulsive effect of atropine had to be controlled by the examination of some of its derivatives and on the other hand, we speculated, that these drugs having proved to be effective on the model convulsive phenomenon, may serve perhaps as new tools in the therapy.

For the investigations 20 tropine derivatives were collected, which had a minimal peripheral ganglionic inhibitory, analgesic and antitremorin effect. Thus the unwated sideeffects could be avoided, and the problems in the interference among different drugs can be reduced to a minimum. For many purposes the tertiary derivatives seem to be most suitable beacuse in case of intravenous application those derivatives have a chance to pass through the blood-brain barriere.

In Hungary NÁDOR and his coworkers (1958) produced tropine derivatives in large series, — and among their materials were found compounds which meet the requirements mentioned above.

A common feature of these derivatives was that the tropine remained either unchanged in them, or its nitrogen-atom was substituted by ethyl- or propyl-groups instead of methyl moiety. Thus our compounds to be examined differed among each other mainly in their acid constituents.

The chemical structures are listed in Table 1.

TABLE 1

NA 181 3-α-phenylacetoxi tropine	0,003	0,05	0,001	∅
NA 184				
NA 184 3-α-diphenyl-acetoxi-tropine	0,002	0,045	0,01	∅
NA 668 3-α-(4 clorid)-bensoiloxi-tropine	0,006	0,006	0,15	∅
NA 676 3-α-diphenly-acetoxi-N-etyl-nortropine	0,006	0,10	0,18	0,075
N 919 3-α-cyclopropylcarbonyloxi-tropine	0,001	0,013	0,06	0,057
N 947 3-α-(9 xanthen)-carbonyloxi-N-ethyl-nortropine	0,01	0,021	0,173	∅

LD_{50} values
(acute mouse-toxicity)

NA 676	71 mg/kg	NA 184	108 mg/kg
NA 668	80 mg/kg	N 919	112 mg/kg
NA 181	105 mg/kg	N 947	113 mg/kg

Of the 20 derivatives subjected to experimental proof only those are reported in this paper which exhibited anticonvulsive action of measurable size.

The effect of the tertiary tropine derivatives was investigated from three points of view:

1. The effect on the rhythmic after-discharge produced by strychnin-neacetylcholine-eserine in the cat's cerebral cortex.
2. The effect on electric convulsions produced by direct epicortical stimulation.
3. The effect on the electroshock of waking rats.

The experiments mentioned under paragraphs 1 and 2 were carried out on cats, superficially anaesthetized by sodium-pentobarbital (40 mg/kg).

The acute toxicity of all derivatives was tested on mice. The toxicity data are given as an addendum to Table 1.

The pharmacological data of six derivatives found to be effective were taken from DECSI's candidate-thesis (1966).

Considering the fact that in some cases also cardiac-effects were seen in the first and second series of the experiments the ECG was registered, too.

The action of the experimental compounds were compared on superficially narcotized cats with a few other drugs, already being used in the therapy to detect any difference in the effect on the chemical and electric conculsions.

The solutions of the therapeutics were made from pure substances obtained directly from the factories, without any substance added.

Methods

Electrocorticography on cats

The animals of both sexes, weighing 1,5—3,00 kg were anaesthetized with 40 mg-kg sodium-pentobarbital given intraperitoneally. One of the femoral veins and the trachea were cannulated. The head of the animal was fixed in a stereotaxic apparatus (Type KOVÁCH) and the brain was

widely exposed on both sides; 2 or 3 ball tipped silver electrodes were placed on each hemisphere and connected to the input of a Galileo Polyphysiograph. Later series of experiments were carried out by use of an eight channel EMG Electroencephalograph. The time constant of the EEG amplifiers was 0,3 sec with an upper limiting frequency of 150 Hz.

One channel of the EEG apparatus served to record the EEG of the animal in the second lead of Einthoven.

Electroshock. Measurement of anticonvulsive activity.

For provoking electroshock on waking rats we used the method of TOMAN, SWINYARD and GOODMAN (1946). The current intensities necessary for provoking maximal seizures were determined on 45 rats. Testing electroshocks were applied in every 48 hours with gradually elevated current intensities. After a 2 week period of testing each animal showed a stable, well reproducible seizure threshold. The scattering of threshold values did not exceed 3 percent. At current strengths of 16—26 m the latency of seizures equalled 3 seconds.

Electric shocks were applied by means of bitemporal electrodes fed from a shocking-device.

After having determined seizure thresholds, the animals were divided into groups; each of them consisted of 5—7 animals. Before administration of the substances to be tested we controlled the seizure threshold by electroshocks given with 48 hours intervals. The dose of the substances was in each case 10 mg/kg body weight given intraperitoneally. 1, 4 and 24 hours after the injection we gave test shocks and the seizure intensities exhibited at these times were compared with the control ones. In cases of substances having long lasting action we made shock tests also after 4—7 days. The complete abolition of seizure we took as an effect of 100 percent, partial seizures were judged to be of 50 or 25 percent according to their intensity. If test shocks produced maximal seizure, the drug action was taken zero. From the values of a group we calculated the mean and this characterized the effectiveness of a substance at a given time after the injection.

Direct stimutation of the brain hemispheres of anaesthetized cats was made as follows. On the exposed medial ectosylvian gyri we placed silver wire stimulating electrodes bilaterally. Square wave pulses used for stimulation had the following parameters: 100 volts, 100 Hz, frequency, 0,7 msec duration. A stimulation period with the above parameters lasted for 5 seconds. At the end of stimulation EEG recording was stharted. The electroshocks provoked in this way had a duration of 15—40 seconds. If the stimulating electrodes were placed on the same side or if we p erformed high decerebration previously no seizure could be obtained.

Provocation of rhythmic after-discharge by pharmacological agents. We placed on the anterior suprasylvian gyrus a piece of filter paper (2×2 mm) soaked in 1% strychnine solution. After the appearance of the strychnine potentials another piece of filter paper was applied to the cortex, soaked in a solution containing 1 percent acetylcholine chloride and 0,1 percent physostigmine sulphate. Under such conditions a rhythmic after—discharge developed in 3—10 minutes, except the anaesthesia was too deep. The drugs tested were given intravenously in this case, too.

The action of tertiary tropine derivatives on the after-discharge elicited pharmacologically

Fig. 1. shows the normal electrocorticogram of a cat in light anaesthesia. The respective locations of the four monopolar leads are indicated in the Figure. The common indifferent electrode was on a frontal skin flap. In Fig. 2. a typical after-discharge is visible provoked pharmacologically in the suprasylvian gyrus. A weak transcallosal projection of seizure is to be seen.

NA 181. The effect of 1,5 mg/kg NA 181 can be seen in Fig. 3. on a rhythmic after-discharge. This dose was capable to abolish an after-discharge of middle intensity in 9 minutes.

The fast rhythmic components disappear completely, only strychnine potentials remain. No substantial change in the electrographic picture of other areas is present.

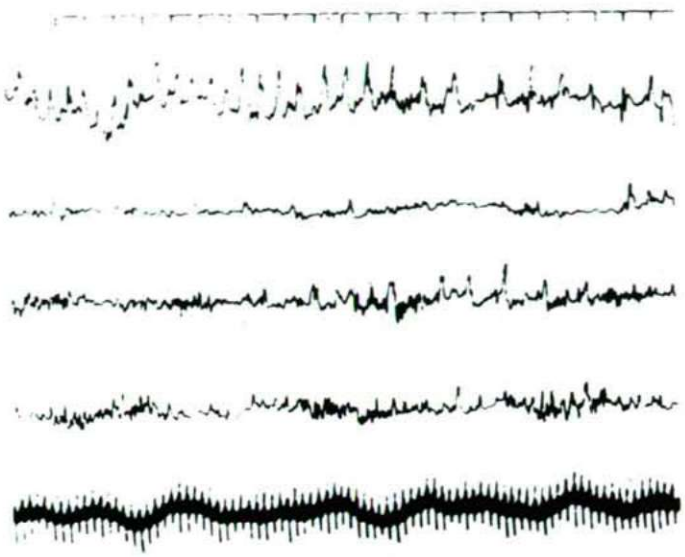

Fig. 1. Electrocorticogram of a cat anaesthetized by 40 mg-kg sodium-pentobarbital. Leads: I.: g. suprasylvius anterior left side, I.: g. ectosylvius medius, left side III.: g. suprasylvius ant. right side, IV.: g. ectosylvius medius right side, V.: Electrocardiogram in II. Einthoven lead. Time marking: 1 s.

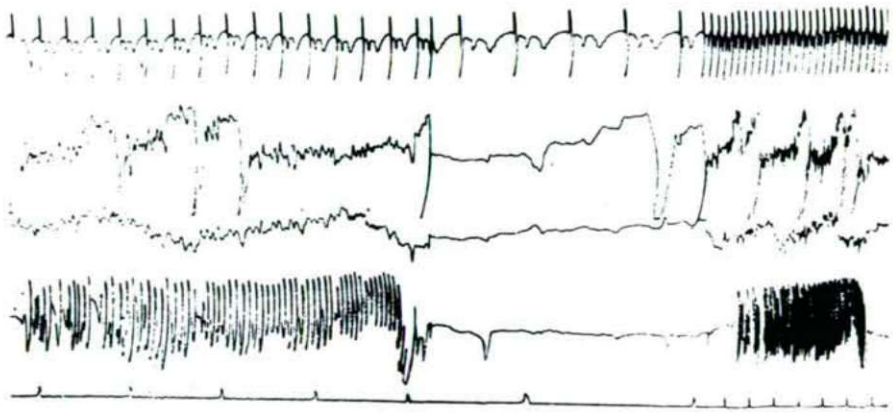

Fig. 2. Rhythmic after-discharge elicited by local application of 1 p.c. Strychnine, 1 p.c. Acetylcholine, and 0,1 p.c. Eserine solutions, on the g. suprasylvius ant, Paper speed at right is higher.

NA 184. The nearest relative of the former compound suppressed rhythmic after-discharges in somewhat higher doses (not illustrated).

NA 668. In Fig. 4. the action of a 2,5 mg/kg dose of NA 668 is demonstrated on a rhythmic after-discharge involving the anterior suprasylvian gyrus. Under drug action the after-discharge was curtailed remarkably, its frequency decreased

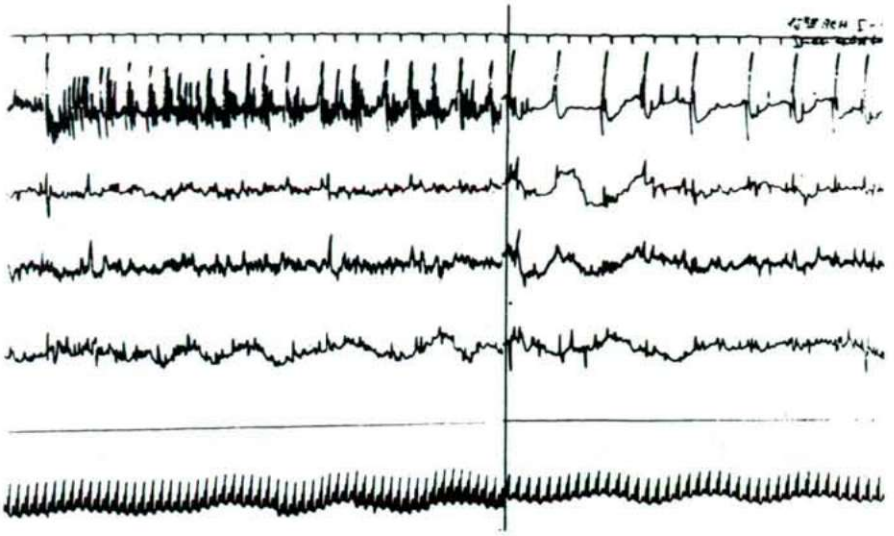

Fig. 3. The effect of 1.5 mg-kg NA 181 on rhythmic after-discharge provoked pharmacologically. At left control, at right 9 minutes after the injection.

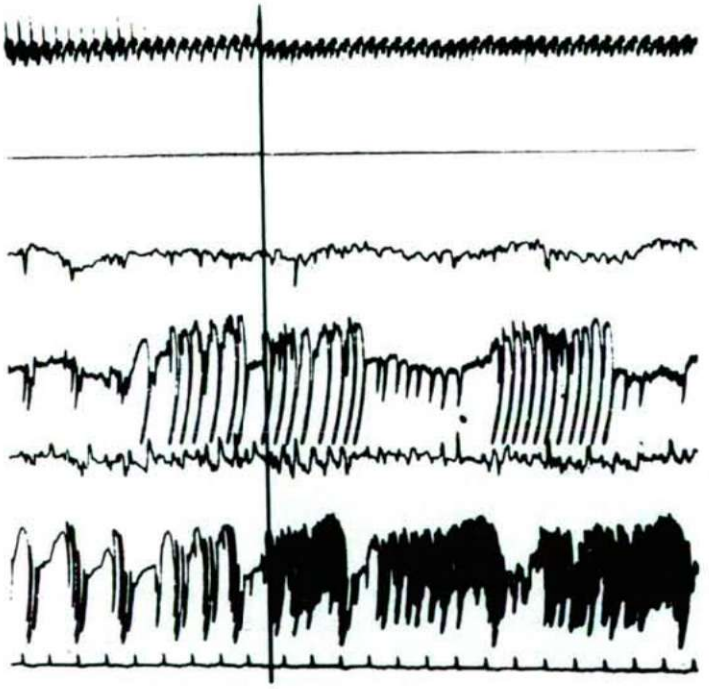

Fig. 4. Rhythmic after-discharge; 2.5 mg-kg NA 668. 5 minutes after injection.

and as only remnants, facilitated strychnine potentials could be seen. The projected strychnine spikes on the opposite side remained intact, too. In the electrocardiogram, there appeared an accentuation of the S-wave.

NA 676. Its effectiveness and type of action was very like to that of NA 668. A dose of 3 mg/kg reduced the after-discharge vigorously in 8 minutes (Fig. 5).

NA 919. Its anticonvulsive activity was weakest of all and 10 mg/kg doses were needed for suppression of after-discharges. The action consisted mainly in the curtailment of the seizure with preservation of isolated strychnine spikes.

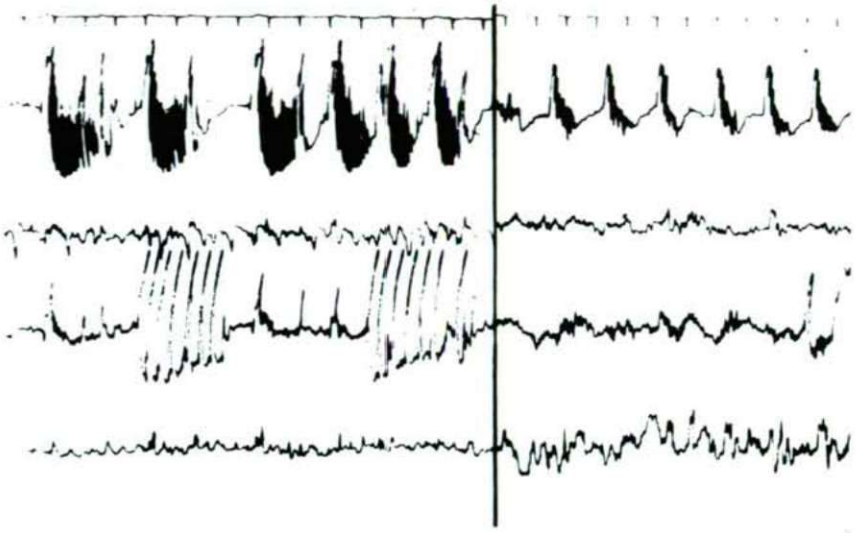

Fig. 5. Rhythmic after-discharge; 3.0 mg/kg NA 676 8 minutes after injection.

N 947. was one of the most potent compounds. The intravenous injection of 1 mg/kg abolished a rhythmic discharge having a projection to the opposite side, too. No remarkable cardiac effects were seen of it.

After this brief demonstration of the actions exerted on rhythmic after-discharges an important comment must be added. Our test-method used in these experiments raised rather rigorous criteria against the drugs tested. One has to consider, that substances provoking seizure discharges were present on the cortex in concentrations ranging from 0,1 to 1,0 percent. (1—10 mg/ml). The compounds tested, given intravenously in 1,5—10,0 mg/kg doses could attain a local concentration in the cerebral tissue not exceeding 1/100—1/1000th of that of the convulsive drugs. Thus they were in a 100—1000-fold drawback as related to the convulsive agents.

Tha action of tropine derivatives on the cortical seizure phenomena elicited by direct stimulation

In the next series of experiments electric convulsions were provoked on the cerebral cortex by means of stimulating electrodes placed on the medial ectosylvian gyri of both sides. The parameters of the stimuli were listed in the Methods. During stimulation the inputs of the EEG apparatus were switched off and recording was started only at the termination of it. The switching-on caused a considerable capacitive artifact, the electric seizure, however subsequent to it, appeared overtly in the record. The electric seizure elicited by a 5 sec stimulation consisted of very fast oscillations of low amplitude, lasting for 15—40 seconds. Its type and duration showed only insignificant variations in the same experiment. Immediately after the seizure the base line was flat, spontaneous activity recovered gradually in 2—3 minutes. Electric seizures could be provoked in every 3—5 minutes with relatively constant duration and electrographic pattern.

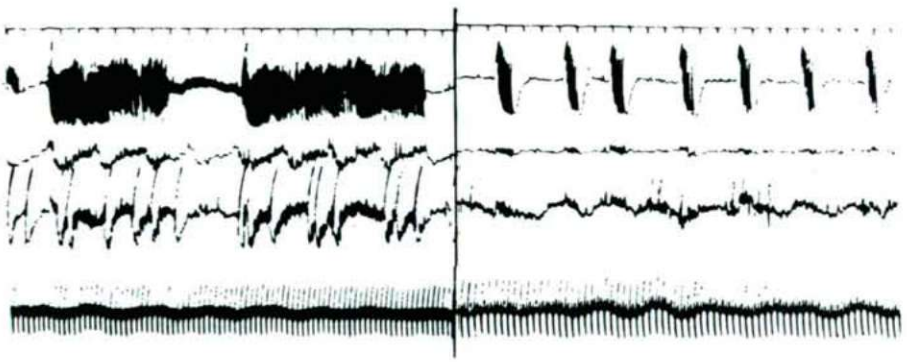

Fig. 6. Rhythmic after-discharge. 1.0 mg/kg N 947. 7 minutes after injection.

In testing tertiary tropin derivatives on the electric seizures we proceeded in the following way. Initially we provoked 3—4 electric seizures with 5 min intervals of rest. Thus the duration and pattern of the seizures characteristic for the animal, was determined. After the last control seizure one of the drugs was injected intravenously in a dose indicated in the respective Figures. (On an animal only one drug was tested.) Afterwards test seizures were elicited in every 5 minutes until the initial seizure pattern recovered. In most animals repeated doses were tested.

In this series of experiments the potency of tropine derivatives was compared with that of the atropine and of several other drugs being in therapeutic use.

Figures 7—10 illustrate the effect of several tertiary tropine derivatives, of atropine and of a commonly used antiepileptic drug.

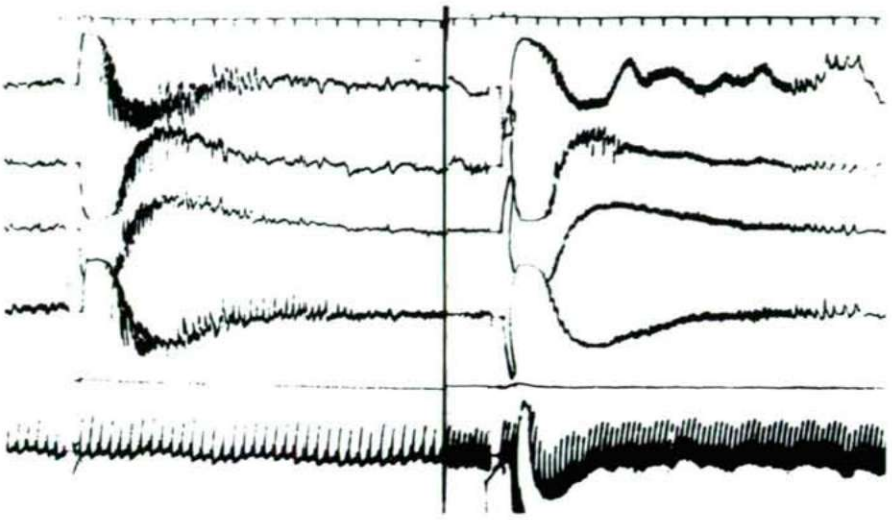

Fig. 7. Cortical electric seizure. At left: control; at right: 7 minutes after injection of 10 mg-kg NA 184.

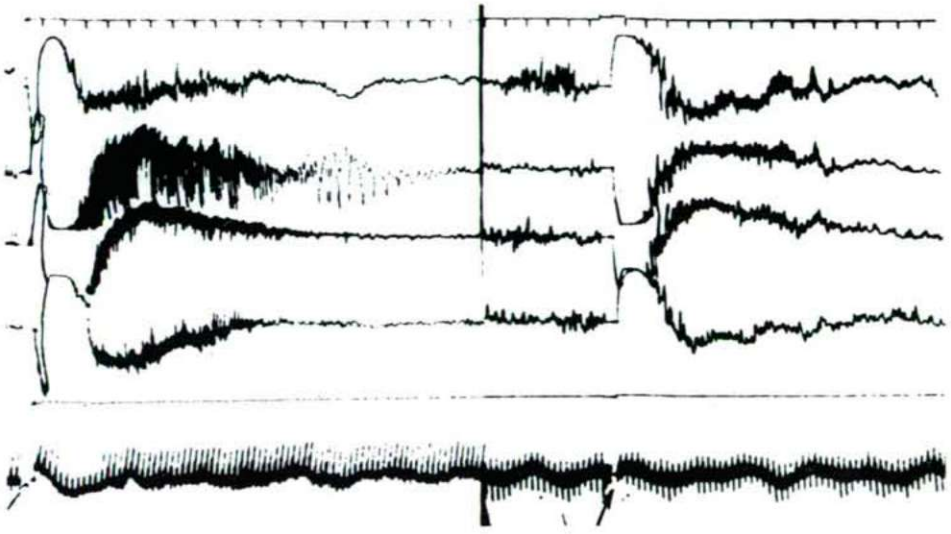

Fig. 8. Cortical electric seizure. 4 mg/kg NA 676; 7 minutes after injection.

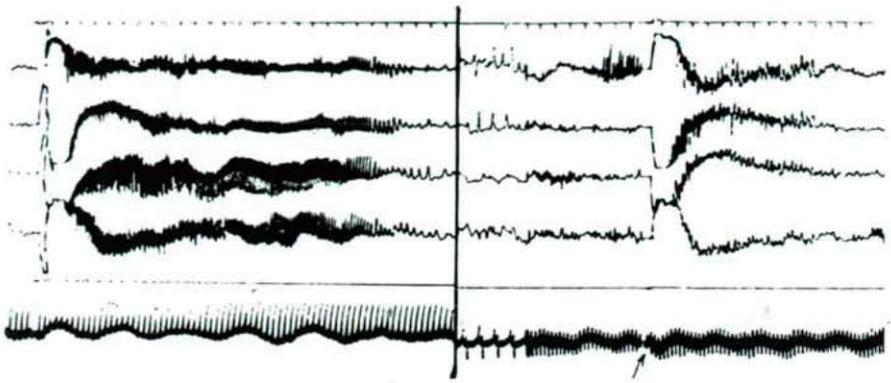

Fig. 9. Cortical electric seizure; 2×1 mg-kg N 947 8 minutes after injection.

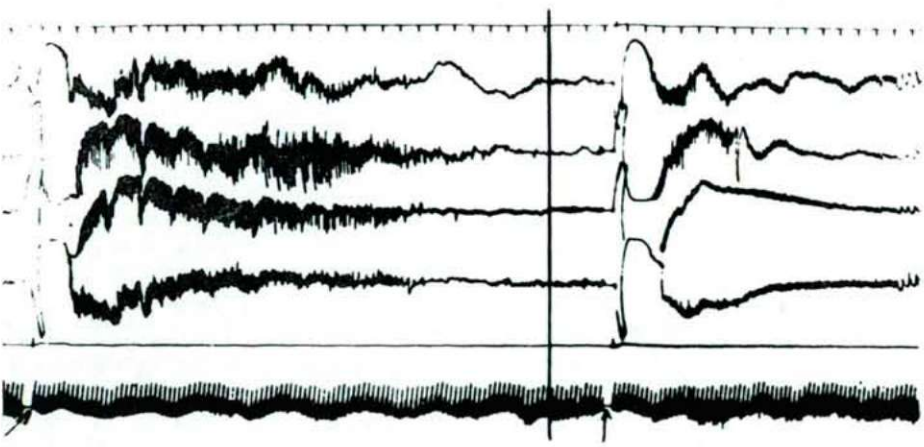

Fig. 10. Cortical electric seizure. 10 mg-kg Diphedan 10 minutes after injection.

The effect of tertiary tropine derivatives on the electroshock of waking rats

By means of the procedure described in "Methods" we provoked electroshock on waking rats. After having determined the seizure threshold, a group of rats was injected with a 10 mg/kg dose of a substance to be tested. Test shocks were givent the end of the 1-st, 4-th, and 24-th hour. In several cases the action could be traced up to the eighthday. The small groups did not allow an exact quantitative evaluation, therefore our data obtained from these experiments give only approximate information about this aspect of the anticonvulsive potency. The time courses and estimated values of the anticonvulsive actions are summarized in Fig. 11.

In the experiments reported here, twenty compounds were examined by each testing procedure. Six of them proved to have any anticonvulsive action. The other substances were either toxic or whitout effect.

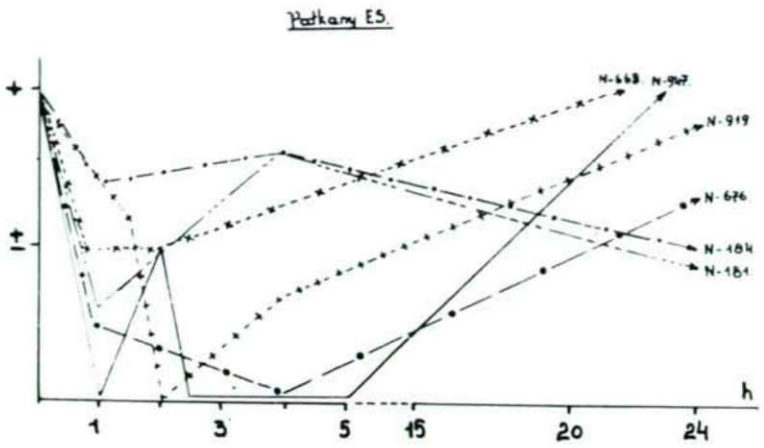

Fig. 11. Approximative anticonvulsive potency of tertiary tropine derivatives as measured on electroshock of waking rats. Ordinate: intensity of seizures; (+) denotes full size electroshock (±) denotes partial electroshock. Points falling on the abscissa denote seizures abolished completely.

Discussion

Before discussing the anticonvulsive effects of tropine derivatives in detail it should be emphasized, that an exact and all round pharmacological analysis of these compounds fell beyond the scope of our experiments. The main purpose of our work was to control the conclusions drawn from earlier experiments and to accumulate a certain amount of qualitative information about this type of compounds in order to make out if they were suitable for further examination as potential therapeutics.

One of the most obvious results of our investigations seems to be, that the compounds tested were much more powerful especially against the acetylcholine induced after-discharge than the drugs commonly used. In case of the electric seizure of the anaesthetized cat the difference was not as expressed. This may have its origin in the mechanism of the acetylcholine induced convulsions. The tropine derivatives may retain some anticholinergic effect of the atropine and thus they may be capable to antagonize cholinergic processes most powerfully. In the electroshock a lot of other than cholinergic mechanisms may be involved. Despite this fact we assume of high importance that six of the compounds tested, proved to be a potent antagonist of electroshock. This latter is commonly accounted a near analogon of human epilepsy.

As to the correlation between the chemical structure and pharmacological action one can propose only assumptions. It leaves no doubt, that the tropine moiety and especially its tertiary nitrogen plays in the formation of the drug-receptor complex, an outstanding role. The chemical nature of the substituent at the tertiary nitrogen seems to be also highly important. By changing the methyl group for an ethyl radical, as it happens in case of NA 184 and NA 676 respectively, an elevation in potency and duration of the drug action could be attined. A further lengthening of the carbon chain of the substituent e.g. by a propyl group is not advantageous.

Also the acidic moiety represents an important constituent of the molecule. Although it is likely to assume that the attachement to the tropine does not leave intact the original pharmacological properties of the acidic moiety, no doubt remains, that the latters will contribute to the overall pattern of the action of the compound molecule.

The phenyl- and diphenyl-acetic acid is a common component of more substances examined (NA 181, NA 184, NA 676).

According to HANSON (1958, 1959) phenyl-acetic acid inhibits glutamic-acid decarboxylase in brain homogenates and in this way reduces the rate of GABA formation. At 100 μM/3,05 ml drug concentration the inhibition may amount to 96 percent. The exact role of the GABA-shunt in the metabolism is not clear, but it is possible that by inhibition of GABA formation the seizure susceptibility may be elevated.

At the same time a depression of the turnover of glutamic acid may impede the overall cell metabolism and thus reducing excitability.

Another, also not easily evaluable set of data comes from FELLMANN (1956) who observed that phenyl-acetic acid inhibits adrenalin synthesis by depressing DOPA-decarboxylase. Although adrenergic mechanisms are not likely to participate in cortical convulsive phenomena, their role in mediation of subcortical influences cannot be excluded.

GARRATTINI and coll. (1958) threw light on the problem form a different point of view. They could show, that both phenyl- and diphenyl-acetic acid inhibit the synthesis of acetylcholine by preventing the acetylation of coenzyme-A. This may be of immediate importance for cholinergic mechanisms. According to FRUENTOW's report, (1963) diphenyl-acetic acid exerted an inhibitory action on serum cholinesterase. LISSUNKIN (1964) observed that both phenyl- and diphenyl-acetic acid combined with vanadyl-sulphate caused to decrease the acetylcholine content of the brain without enhancing cholinesterase activity. Dann and SUCKER (1964) report about diphenyl-acetic acid and xanthen-9-carbonic acid to have a spasmolytic effect, in which, in the autors' opinion, the inhibitory action upon acetate activating enzymes, plays a definite role. In accord with the data cited previously SZADOVSKA and coll (1964) found not only spasmolytic but also hypotensive effects of esters of diphenyl-acetic acid. These compounds inhibit histamine-contracture of the guinea pig ileum and some of them have analgesic action, too. MEDAKOVIĆ and BANIČ (1963) reported about potentiating effects exerted by some derivatives of the phenyl-acetic acid (CFT 1201 and 1208) on the analgesic action of morphine.

DOYLE and coll. (1965) described expectorant, anti-cholinergic and narcosis-potentiating effects of alcoxymethyl and thiol esters of diphenyl-acetic acid.

A more general picture was given about the effects of phenyl-acetic acid by HICKS and coll (1964) who stated that it inhibited the respiration of the brain tissue, and a wide variety of enzymes, (monoamino-oxydase, glutamic acid decarboxylase, dioxyphenylalanine- and 5-hydroxytryptophane decarboxylase, lactic acid dehydrogenase, glutamic acid- oxalacetic acid- and pyruvic acid- transaminase).

As it is evident from this review far from completeness, phenyl- and diphenyl acetic may influence cellular metabolism in a variety of ways and most of these point to a suppression of cellular activity. The question, however, remains uncleared whether their combination with tropine results in any modifications of the original

pharmacological effects. The tropine itself is assumed to combine with membrane receptors. Its esters behave very likely in analogous manner. This may alter profoundly the pharmacological properties of the acidic moiety. The penetration of tropine esters through the cell membrane awaits to be claered up.

Essentially the same can be told of xanthen-9-carbonic acid and its derivatives. This compound is a component of the substance labelled N 947. The spasmolytic, anticholinergic and antihistaminic effects of these compounds have been shown by several authors (GOLDBERG and WRAGG, 1957, 1960; LIEBER, 1957). We assume that these potencies contribute to the remarkable anticonvulsive action of N 947.

In case of N 919 it is not easy to decide at what extent the acidic moiety plays a role in the final action. The cyclopropane was a widely used anaesthetic (WORINGER and coll, 1951; HAID, 1953; RIKER and coll, 1959) having a presumably analogous mechanism of action with that of other inhalation anaesthetics. It is hardly conceivable that an action being physicochemical in nature could be preserved in that of a compound molecule. About the pharmacological effects of the cyclopropyl-carbonic acid no data are available.

Summing up the results and conclusions presented above it can be stated that there exist remarkable correlations between the chemical structure and pharmacological actions of the tertiary tropine derivatives examined by us. Our experiences may yield fruitful ideas for the synthesis of new potent drugs of this type.

Our conclusions may be summarized as follows.

1. The attachment of the molecule to the appropriate receptors of the neural substrate is made possible by the N-methyl group of the tropine.

2. The duration of the effect is lengthened by N-ethyl substitution. This seems to confirm the assumption included in issue 1.

3. Only tertiary derivatives can be taken into account as anticonvulsive drugs because thay have a chance to penetrate the blood brain barriere.

4. Making a choice of the acidic moiety one has to prefer the ones having similar effects to those wanted from the tropine ester.

5. As tropine esters are not likely to enter the cell they do not interfere with metabolic processes. Therefore chronic toxic effects (autoagressive diseases, injuries of the liver and bone marrow) do not represent a real danger as they do in case of the antiepileptic drugs being in use.

As to the mechanism of action only hypotheses can be put forward. The assumption, however, seems to be justified, that most of them exerts its action by virtue of its anticholinergic potency. Our knowledge about the role of cholinergic synapses in convulsive phenomena is very scarce. The only that can be assumed, is, that a blockage of the depolarizing effect of acetylcholine may be the critical moment at which tropine derivatives interfere with seizure activity. This may be realized by preventing depolarization block of inhibitory neurones and by depressing the overall excitability of cortical cells either. The latter assumption seems to be invalidated by the fact, that tropine derivatives are against strychnine potentials or tetracor seizure without effect. Their excellent protective action against electroshock, however, on anaesthetized cats and waking rats, gives some hope that this type of compounds, may be axpected synthetized, and will contribute effectively to the strugle against human epilepsy.

Literature

DANN, O., SUCKER H. (1962): Spasmolytisch wirksame Ester und deren Säuren als Hemmstoffe azetat-aktivierender Enzymen. — Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *295-65*, 497—504.

DECSI, L. (1966): Vizsgálatok az idegrendszerre ható szerekkel. Kandidátusi értekezés.

DOYLE, F. P., MEHTA, M. D., WARD, R., BAINBRIDGE, J., BROWN, D. M. (1965): Chemie und Pharmacologie einiger Ester von basischen Alkoholen. — J. med. Chem. *8*, 571— 76.

FEHÉR, O., HALÁSZ, P., MECHLER, F. (1965): The mechanism of origin of cortical convulsive potentials. Electroencephal. — Neurophys. *19*, 541—548.

FELLMANN, J. H. (1965): Die Hemmung von DOPA-Decarboxylase durch in Verbindung mit Phenylbrenztraubensäureoligophrenie auftretende aromatische Säuren. — Proc. Soc. exp. Biol. Med. *93*, 413—414.

FRUENTOW, N. K. (1963): Bedeutung der Kationengruppe und ihrer Stellung im Molekül für die Reaktion des Substrates un der reversiblen Inhibitoren mit der Cholinesterase. — Biochimija *28*, 964.969.

GARATTINI, S., MORPURGO, M., PASSERINI, N. (1958): Eine Reihe neuer Verbindungen, welche die Cholinacetylierung hemmen. — Experientia (Basel). *14*, 89—91.

GOLDBERG, A., WRAGG, A. H. (1957): Vom Xanthen abgeleitete Spasmolytica. — J. Amer. chem Soc. — *79*, 4226—4229 5/8.

GOLDBERG, A., WRAGG, A. H. (1960): Vom Xanthen abgeleitete Spasmolytica. — J. chem. Soc. (London) 543—455.

GYERMEK, L. (1957): Toxicitási vizsgálatok. — Kísérletes Orvostud. Vizsg. Módsz. *3*, 854—881.

GYÖRGY, L., DÓDA M., NÁDOR K. (1961): Die Bedeutung quaterner Gruppen verschiedener Raumerfüllung für den parasympathicolytischen und den Ganglien-blockierenden Effekt der Tropine. Arzneim. — Forsch. (Drug. Res.) *11*, 444—448.

HAID, B. (1953): Die Cyclopropannarkose. Anaesthesist. — *2*, 128—131 Ang.

HANSON, A. (1959): Die Wirkung von Phenylalaninmetaboliten auf Glutaminsäure-Transaminase in Hirn. — Acta chem. Scand. *13*, 1366—1374.

HANSON, A. (1958): Hemmung der Hirn-Glutaminsäuredecarboxylase durch Phenylalaninmetaboliten. — Naturwissenschaften *45*, 423.

HICKS, J. M., YOUNG, D. S., WOTTON, I. D. (1964): Die Wirkung uremischer Blutkonstituenten auf bestimmte Hirnenzyme.[1]— Clin. chim. Acta (Amsterdam) *9*, 228—235.

LIEBER, C. S. (1957): Vergleichende Untersuchung über die hemmende Wirkung des Atropins und zweier synthetischer Parasympathicolytica auf die Magensaftsekretion. — Ann. Soc. roy. Sci. med. natur. (Bruxelles) *10*, 209—321.

LISSUNKIN, J.n I. (1964): Der Acetylcholin-Stoffwechsel des Rattenhirns bei kombinierter Einwirkung von Vanadylsulfat und einigen Phenylessigsäurederivativen. — Bull. Exp. Biol. Med. (UdSSR) *57*, (29.) 2, 80—83.

MEDAKOVIC, M., BANIC, B. (1963): Der Einfluss von zwei Phenylessigsäurederivaten auf die analgetische Wirkung von Morphin in Mäusen. — J. Pharmacy Pharmacol. *15*, 660—665.

NÁDOR, K. (1958): A gyógyszerkutatás elvi problémái. — MTA Biol. Oszt. Közleményei. *8*, 187—216.

RIKER, W. F., WERNER, G., ROBERTS, J., KUPERMAN, A. (1959): Pharmacologischer Beweis für die Existenz eines präsynaptischen Vorgang bei der neuromusculären. Übertragung. — J. Pharmacol. exp. Ther. *125*, 150—158.

WORINGER, E., BROGLY, G., SCHNEIDER, J. (1951): Untersuchung der Wirkung allgemein gebräuchlicher Anästhetica auf den Druck der Rückenmarksflüssigkeit. Praktische Bemerkungen auf ihre Verwendung in der Nervenchirurgie. — Anesthésie et Analgésie *8*, 649—662.

Address of the authors:
Prof. Dr. O. FEHÉR
G. A. BÁLINT
Á. BALOGH
Department of Animal Physiology
A. J. University,
H—6701 Szeged, P. O. Box 428.,
Hungary