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THE INFLUENCE OF TOPICAL ADMINISTRATION OF β -CARBOLINE DERIVATIVES ON DIRECT CORTICAL RESPONSE (DCR)

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By means of DCR, the influence of 1-methyl (A), 2-pyridyl (B) and 4-pyridyl (C) β -carboline derivatives on the following types of cortical electrogenesis has been studied: 1) primary negativity which is an expression of activity of axodendritic synapses, 2) positive peak, which is probably mainly caused by activity of axosomatic synapses. Experiments were carried out with 34 cats of both sexes, weighing 2,5—3,0 kg., under general chloralose anesthesia. Carboline derivatives were applied to the cortex on pieces of impregnated filter paper.

The experiments were concerned with the following problems: 1) determination of the magnitude of the pharmacological effect in relation to structure of the carboline derivatives. Activity of the carboline derivatives decreased, in relation to the all types of electrogenesis, in the order B, C, A, 2) plotting of a „dose response“ curve for the most active derivative, B used in concentrations 10^{-3} , 10^{-4} and 10^{-5} g/ml, 3) determination of the relation between the size of the dose and that of depressing effect of the first negative peak 2 min after stimulation.

The β -carboline derivatives block axodendritic synapses and exert a facilitating action on axosomatic synapses.

DCR, which is a complex reaction of the neocortex, consists of a negative wave or so-called superficial response of Adrian, and a positive peak, or deep response. Each component of DCR presumably depends on different, spatially remote, neuron groups, or on different type of central synapses. Each component is an expression of a different type of electrogenesis. Studies on the influence of chemical compounds on the different components of the DCR allow their localization and determination of the probable mechanism of their action, i.e. their neuropharmacological character.

By means of DCR, attempts have been made to determine the pharmacological nature of the pharmacological action of serotonin, which is a mediator in chemical transmission in the CNS [5, 6], but unequivocal results have not been achieved. Depending on the concentration of serotonin and the method employed (examination of intact cortex or of sections of the cortex), various effects were observed [3]. On the whole, it is agreed that serotonin suppresses DCR, but marked discrepancies exist pertaining to the sensitivity of different peaks of DCR. Ochs et al. [5] after epicortical point administration of $5 \cdot 10^{-3}$ — $1 \cdot 10^{-2}$ g/ml of serotonin observed decrease or abolition of the negative component of DCR, indicating an influence of this neurohor-

more on postsynaptic potentials from the apical dendrites of pyramidal cells. The use of serotonin is attended by additional difficulties of interpretation due to the direct action of this compound on the cell membrane, especially on synapses, or indirect mechanisms acting through changes in blood circulation.

The aim of this study was to determine the neuropharmacological synaptic action of some carboline derivatives by means of DCR. Observations indicate that carboline derivatives being antagonists of serotonin easily penetrating the blood-brain barrier and having no influence on the blood circulation, act directly on neurons [7—9].

MATERIAL AND METHODS

Acute experiments were carried out on 26 cats of either sexes, weighing 2.5—3.0 kg. Under chloralose anesthesia, the skull was opened and a piece of the dura 1.5—2 cm was removed. Electrical and chemical stimulation and recording of evoked potentials were performed on the gyral cortex (the cortex in the sulci was not taken into account).

Signals from the brain were transmitted to the input of a Grass polygraph (model 5D9, consisting of a preamplifier (5P5) and amplifier (15E)). Amplified DCR from the second stage of the amplifier were transmitted to a Tektronix (type 502) oscilloscope. Single or superposed runs were photographed with a Kymograph-Grass (model C-4-K) film camera. Electrical stimuli lasting 0.1 msec from a Grass stimulator (type S4G) had not voltage but intensity character; resistance giving current in the range 0.5—1.5 mA were connected with the output of an isolation unit (SIU-4B).

Chemical stimulation was performed by the topical administration for a period of 2 min a piece of filter paper (2 × 2 mm) impregnated with a solution of β -carboline derivatives, placed on the lateral and supramarginalis gyri between the stimulating and recording electrodes.

The first recording electrode was 4 mm and the second 8 mm distant from the site of electric stimulation. Experiments were performed with three carboline derivatives (6-methoxy-1,2,3,4-tetrahydro- β -carbolines) which had the following substituents at the position 1: A = methyl, B = 2-pyridyl, C = 4-pyridyl. Carboline derivatives A, B and C were used at concentrations 10^{-6} – 10^{-8} g/ml. Solutions pH was 5.7, — for A; 6.8 — for B; 5.2 — for C. Solutions alcalized to pH 7.0 with 0.01 N NaOH did not change their physical properties. Filter paper pieces impregnated with physiologic NaCl solution served as the control.

The experiments were concerned with the following problems: 1) determination of the magnitude of the pharmacological effect and its relation to the structure of the carboline derivatives, 2) construction of a „dose-response“ curve for the relation between the size of the dose and time of appearance of reversed polarity of the first negative peak of DCR. The standard deviation was calculated for some results.

RESULTS

The investigated carboline derivatives, irrespective of the type of substituent, exerted a qualitatively similar effect on DCR, consisting in suppression of the response preceded by decrease of the negative peak of the response. After 15 min. DCR returned to the previous situation.

Owing to different structural details of their molecule, the carboline derivatives elicited quantitatively different changes in DCR. The average pattern

of the action of the compounds calculated on the basis of results of 36 experiments, is illustrated in Fig. 1. Derivative B exhibited the highest activity; 5 min after application the response was suppressed to 28% of the starting

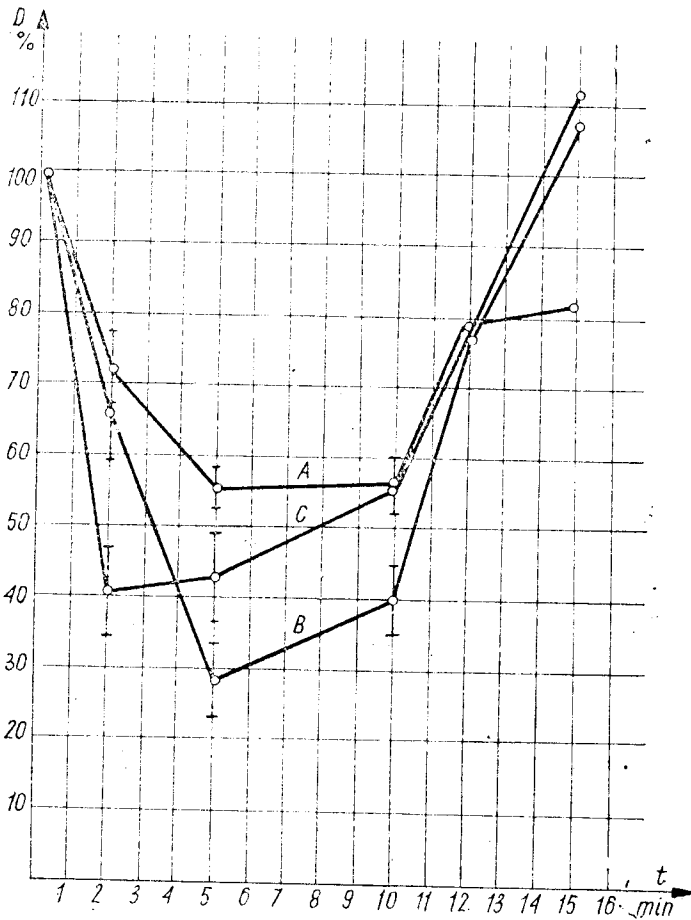


Fig. 1. Average pattern of the effect of A, B and C on DCR. Time is plotted on the abscissa, on the ordinate-amplitude of the negative peak of DCR. Amplitude of the initial responses taken as 100%. The standard deviations marked as the perpendicular segments for the main points.

value. Derivative A showed the weakest activity, amplitude of the first peak of the response was reduced to 56% of the starting potential. Derivative C reduced the induced function potential to 43% of the starting value. The course of the effect of all three carboline derivatives, on the other hand was similar. Fifteen minutes after application of A and C, compensatory increase of the dimensions of DCR was observed; after B which produced the greatest depression, 15 min was too short a period for complete recovery of DCR to the starting state.

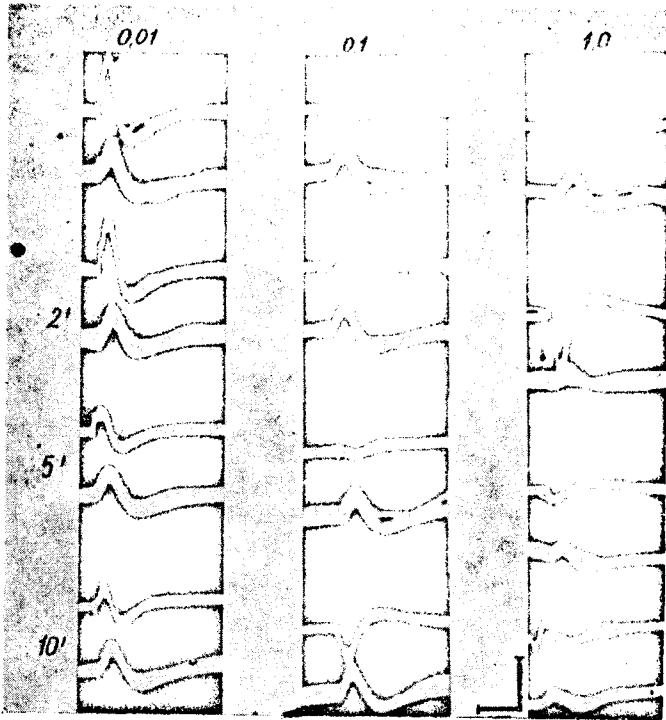


Fig. 2. Cat 23. Effect of different concentrations of B on DCR. Upper trace comes from the closer electrode, lower one from the more distant electrode. Concentration in mg/ml given at the top of each column. Time marked at the left side. Horizontal line — 20 ms; vertical — 100 μ V.

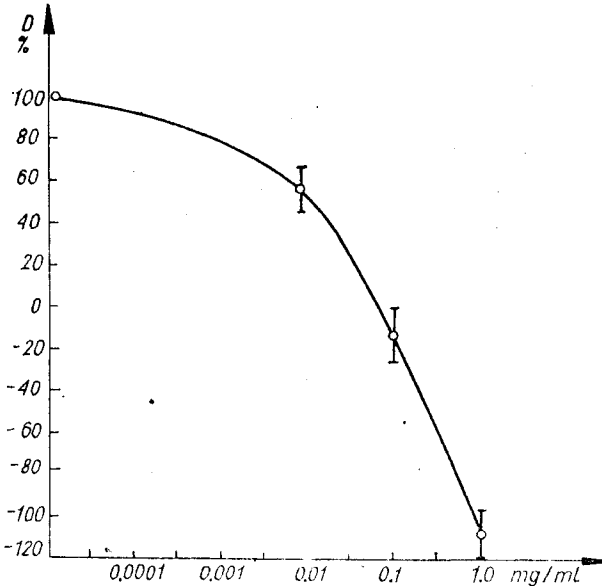


Fig. 3. Average pattern of the relation between concentration of B (abscissa) and size of the negative peak of DCR (ordinate). Amplitude of the initial responses taken as 100%. The standard deviations shown by the perpendicular segments calculated for the main points.

The relation between concentration and magnitude of the pharmacological effect was determined with the most active derivative B. When evaluating the pharmacological effect, only the superficial — negative wave was taken under consideration, which is the most sensitive component of DCR, undergoing

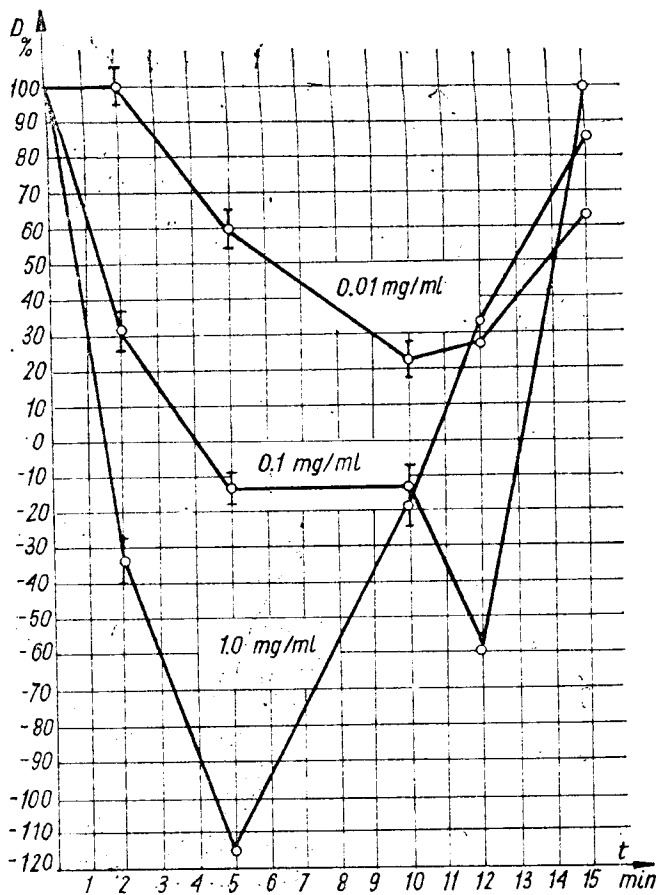


Fig. 4. The relation between the depressing effect and the concentrations of B after the same time. (Points recalculated from the Fig. 1).

constant and the earliest depression or reversal of polarity. The compound was used in concentrations 10^{-5} , 10^{-4} and 10^{-3} g/ml. Fig. 2 shows that the depressive effect of compound B increases in proportion to its concentration. The lowest concentration reduced only the amplitude of the negative peak. Tenfold increase of the concentration caused reversal of polarity of the first peak of the response, preceded by a phase of complete flattening. The concentration of 10^{-3} g/ml not only influenced the response from under the nearer electrode giving the pattern of reversed polarity, but also markedly lowered

the potential of the response from the electrode placed farther from the site of stimulation.

The character of the „concentration-response“ relation is illustrated in Fig. 3, which shows that in proportion to the logarithmic concentration of B, the depressing pharmacologic effect increases approximately proportionally in arithmetic progression.

The dynamic characteristics of DCR changing under the influence of B applied in different concentrations are presented in Fig. 4.

On the basis of Figs. 2 and 4 the relation between concentration and time of reversal of polarity of the negative peak can be determined. The smallest concentration produced no change in polarity but the flattening of the negative wave.

The concentration 10^{-4} g/ml, 10 min after application reversed polarity, showing intermediate phases. The application of the solution with 10^{-3} g/ml concentration reversed the sign of the first peak after 2 min without showing intermediate phases.

DISCUSSION

The carboline derivatives have an uniformly depressing effect on the first, negative component of DCR, and at the same time cause an increase of the positive peak. The superficial — negative wave of postsynaptic, dendritic origin arises in the synaptic structures, which according to Grundfest [2] are electrically insensitive. It is thought to be a mixture of two types of electrogenesis: negative of the relatively higher amplitude and positive of relatively smaller potential value. The chemical compound acting on exodendritic synapses may disturb the relations between the two types of electrogenesis. Carboline derivatives shift the balance toward the side of positive electrogenesis, blocking the presumably excitatory axodendritic synapses and consequently causing flattening of the negative peak or even reversal of polarity.

According to another explanation [1], the positive peak, being an expression of summation of bioelectric activities of axosomatic synapses, is normally masked by the activity of superficial cortical layers. Carboline compounds abolish electrogenesis of elements in the upper layers of the cerebral cortex, and thus the superficial-positive wave from deeper cortical layers may be revealed.

A direct action of carboline derivatives on cell membranes of neurons and central synapses is suggested by the curves showing the relation between the size of the pharmacologic effect and the concentration of the studied compounds.

The effect of the carboline derivatives was similar in substance to the effect of serotonin on DCR described by Ochs et al. [5]. The lowering of the ampli-

tude of the negative peak of DCR after serotonin, an „inhibitory synaptic neurohumor“ [4] and the same effect after carboline compounds may be regarded as a disturbance of the transmitter processes in the cerebral cortex.

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WPLYW NAKOROWYCH PODAŃ POCHODNYCH β -KARBOLINY NA BEZPOŚREDNIE ODPOWIEDZI KOROWE (DCR)

Streszczenie

Za pośrednictwem bezpośrednich odpowiedzi korowych badano wpływ 1-podstawnych 6-metoksy-1, 2, 3, 4-tetrahydro- β -karboliny: metylowej (A), 2-pirydylowej (B) i 4-pirydylowej (C) na: 1) pierwotny ujemny załamek, który ma być wyrazem czynności styków aksodendrytycznych, 2) na fałę dodatnią, która prawdopodobnie pochodzi od synaps akso-somatycznych.

Doświadczenia przeprowadzono w narkozie chloralozowej na 34 kotach, obojga płci ważących 2,5—3,0 kg. Roztwory pochodnych karbolinowych podawano nakorowo w postaci przymoczek bibułowych.

Doświadczenia miały na celu: 1) określić wielkość farmakologicznego efektu w zależności od struktury pochodnych karbolinowych. Działanie farmakologiczne w odniesieniu do obydwóch typów elektrogeneracji malało w porządku B. C. A; 2) wykreślić krzywą „dawka-odpowiedź“ dla najaktywniejszej pochodnej (B) używanego w stężeniach 10^{-3} , 10^{-4} , 10^{-5} g/ml; 3) określić stosunek między wielkością dawki, a rozmiarami wpływu depresyjnego pierwszego ujemnego załamka 2 min. po podrażnieniu. Pochodne karbolinowe blokują aksodendrytycznie styki, a wywierają wpływ ułatwiający na synapsy akso-somatyczne.

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ВЛИЯНИЕ ДОЗИРОВАННЫХ НА КОРУ МОЗГА β -КАРБОЛИНОВЫХ ПРОИЗВОДНЫХ НА НЕПОСРЕДСТВЕННЫЕ КОРОВЫЕ РЕАКЦИИ (DCP)

Содержание

Посредством непосредственных коровых реакций исследовалось влияние 1-производных 6-метоксы-1, 2, 3, 4-тетрагидро- β -карболины: метиловой (A), 2-пиридиловой (B) и 4-пиридиловой (C) на: 1) первичное отрицательное преломление, которое должно быть выражением действия аксо-дендритических контактов; 2) на положительную волну, вероятно производимую от аксо-соматических синапс.

Опыты проводились в хлоралозовом наркозе на 34 кошках, обоего пола, с весом 2,5—3,0 кг. Растворы карболиновых производных подавались на кору в виде примочек на фильтровальной бумаге.

Опыты проводились с целью: 1) определить фармакологический эффект в зависимости от структуры карболиновых производных — фармакологическое воздействие по отношению к обоим типам электрогенеза уменьшалось в очередности B, C, A; 2) начертить кривую „доза — реакция“ для самой активной производной (B) применяющейся в концентрации 10^{-3} , 10^{-4} , 10^{-5} г/мл, 3) определить соотношение между дозой и депрессивным влиянием первого отрицательного преломления в 2 минуты после раздражения. Карболиновые производные блокируют аксо-дендритические контакты, и имеют облегчающее влияние на аксо-соматические синапсы.

REFERENCES

1. Eccles J. C.: Structure and function of the cerebral cortex. Ed. Tower D. B., Schade J. P. Elsevier 1960, 192.
2. Grundfest H.: Neuropharmacology. Ed. Bradley P. B., Flugel F., Hoch P., Elsevier 1964, 3, 245.
3. Mantegazzini P.: Handbook of Experimental Pharmacology. Springer Verlag, Berlin 1966, 19.
4. Marazzi A. S.: Ann. N. Y. Acad. Sci., 1957, 66, 496.
5. Ochs S., Brooker H., Aprison M. H.: Physiologist 1960, 3, 121.
6. Stefano Di V., Leary D. E., Feldman I.: Proc. 1956, 15, 417.
7. Trąbka J.: Dissert. Pharm., 1964, 14, 419.
8. Trąbka J.: Dissert. Pharm., 1965, 17, 417.
9. Trąbka J.: Dissert., Pharm. Pharmacol., 1966, 18, 539.

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