PHARMACOLOGY

THE INFLUENCE OF BULBOCAPNINE ON BEHAVIOR AND ON CEREBRAL ELECTRICAL ACTIVITY IN THE CAT

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Although bulbocapnine has been known for several decades [6, 9] during which time it has been widely studied by psychiatrists, neurophysiologists, and biochemists very little work has been done until now to determine its site of action. We know neither at what level it acts, nor even whether its initial action is on cells of the central nervous system [7], nor whether it is a muscle toxin [5, 10]. De Jong [7] emphasizes the effect on the cortex, while Schaltenbrand and Cobb [11] have shown from their experiments carried out on decorticate preparation that catalepsy may be induced quite independently of the cerebral cortex. Later de Jong admitted that the action of bulbocapnine might not be confined to the cerebral cortex but might act also at other levels of the central nervous system. In his opinion bulbocapnine causes asphyxia in the cells of the central nervous system. Thus at the present time there are several opinions concerning the site of action of bulbocapnine.

Until now views concerning the nature of the action of this toxin have been at variance, i.e. it has not been clear whether it exerts an excitatory or an inhibitory action on nerve cells. Changes in electrical activity indicate a preponderance of excitation in all cortical and subcotrical structures investigated, whereas studies on the threshold of excitability in different parts of the central nervous system and work on the nature of the changes in higher nervous activity indicate that bulbocapnine exerts an active inhibitory influence [1-4, 8].

The object of the present investigation has been to determine as completely as possible the influence of bulbocapnine on the behavior and electrical activity on the brain in order to establish the nature of the central action of this substance.

EXPERIMENTAL METHOD

The experiments were carried out on 11 cats of both sexes; no use was made of curare. Electrodes were permanently implanted into the following cortical and subcortical structures: the neocortex (motor and visual cortices), the arthicortex (hippocampus), the amygdala, the septal region, the caudate nucleus, the reticular formation of the thalamus and mid brain, and the hypothalamus. The electrodes were implanted by use of a Horsley-Clarke stereotaxic apparatus; co-ordinates were obtained from the atlas by Jasper, and subsequent histological control confirmed their correct placement.

The bulbocapnine was prepared by the All-Union Institute of Medicinal and Aromatic Plants from fumitory (Coridalis marshalliana). We injected from 4 to 100 mg/kg subcutaneously. Behavior and EEG studies were made on the same animal. Initially behavior studies were made under normal conditions of autonomic functions, reactions to stimuli of various modalities; we also studied the electrical activity of different parts of the brain.

EXPERIMENTAL RESULTS

The behavioral changes could be classified as follows: 1) motor, 2) autonomic, and 3) emotional disturbances.

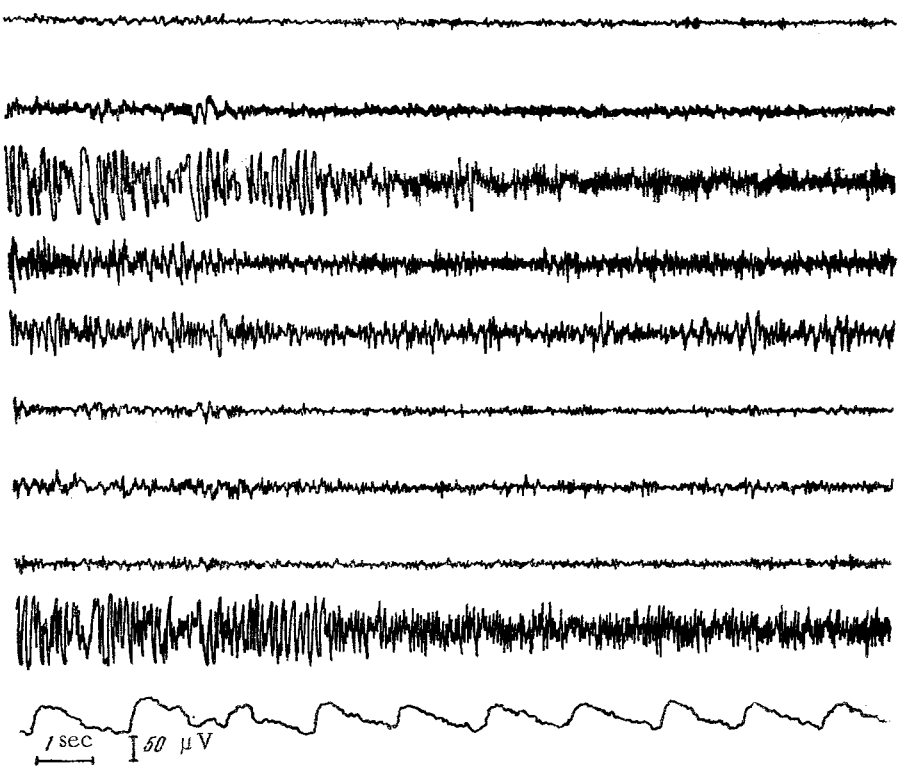

Fig. 1. Prolongation of the "waking" state in the EEG of a cat during bulbocapnine poisoning. Curves, top to bottom: septal region, caudate nucleus, motor cortex, hippocampus, amygdala, hypothalamus, reticular formation of mid brain, medial thalamic nuclei, visual cortex. —respiration.

The minimum dose of bulbocapnine (4 mg/kg) used in our experiments was sufficient to evoke noticeable behavioral changes. After 15-20 min the animal became inhibited, its movements were slowed, it crept into a corner or under a cupboard or table and always turned its face to the wall. At this time there were no signs of catalepsy or of enhanced muscle tone.

Rather larger doses (8 mg/kg) produced a different picture: after 15 min a definite catalepsy and stupor developed. The body could be placed in any grotesque position, which was then maintained for a long time. Further increase of the dose did not change the type of behavior, but merely caused the condition to be longer maintained. The motor disturbances described above were of a hypokinetic nature; there was no tremor or convulsions (even with very large doses).

As a rule the initial signs developed 3 min after the injection; there was a marked autonomic disturbance, which might be of various degrees of intensity; they were not directly related to the dosage. The disturbances were both sympathetic and parasympathetic: there was a profuse salivation, vomiting, occasional diarrhea, tachycardia, and a marked mydriasis, which was sometimes asymmetrical. The respiratory disturbances consisted not so much of a relative increase in rate (30 instead of the normal 18) as of a change in the ratio of the duration of inspiration to expiration. For example in a respiratory cycle lasting 2.2 seconds, inspiration lasted 2 seconds and expiration 0.2 seconds. All the autonomic disturbances we have described occurred chiefly at the start of the pathological process.

We paid particular attention to the characteristic "emotional" reactions in cats, which developed during the catatonia. Although we were unable to study the emotional manifestations we nevertheless think it useful to describe some of the characteristic reactions. They were always of the same type, that is to say negative, and they appeared in response to any dose of bulbocapnine. At the start the animals experienced fear reminiscent as far as its external manifestations were concerned to behavioral features in human beings. Initially there were distressful sounds. At the very onset of the condition these sounds were in the nature of a reaction, that is to say they developed only in response to stimuli (approach of experimentor, attempt to place the animal in some artificial pose, needle prick, or sounds). As the condition advanced, and particularly at the peak of the condition the sounds were emitted spontaneously, or

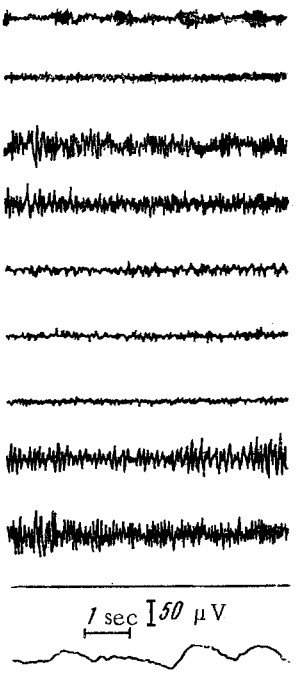

Fig. 2. Burst of high-frequency spindles in the septal region during the action of bulbocapnine. Indications as in Fig. 1.

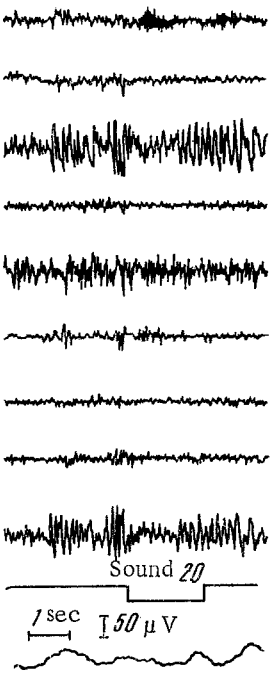

Fig. 3. Bursts of high-frequency discharges in the septal region and in the hypothalamus during desynchronization in the cortex. Indications as in Fig. 1.

at any rate without any visible external stimulus. The condition of fear and anger was also shown in the characteristic facial expressions. After the injection of bulbocapnine, as the cats became immobile they assumed the expression of "consternation" ("goggle eyes"); their petrified gaze was combined with wide pupillary dilatation and their hairs and whiskers drooped. Gradually the "consternation" was replaced with an expression of fear and "suffering." This emotional upset continued as long as there were any effects and disappeared together with the motor disturbances.

The question of the extent to which the animal can react during bulbocapnine poisoning deserves special attention. We were unable to determine definitely whether the sensitivity to external stimuli was lowered or raised. The animals behavior indicated that at the very onset of the changes the reactivity was enhanced, but as the action of the drug increased the animals almost ceased to react. At this stage it was difficult to determine whether they perceived the stimuli less distinctly, or whether it was that any external manifestation on their part of what they perceived had become reduced through reduction of motor activity.

Numerous studies of the electrical activity of the feline brain has been made, and therefore we will not deal in detail with the normal electrical potential. We will merely note that if a prolonged record of the activity is made in complete silence in a darkened room the cat slumbers from time to time. Accordingly spindles characteristic of sleep are recorded from time to time. During the waking state the EEG displays arrhythmic and chiefly rapid spikes. The voltage in the cortical regions varies between 30-100 and 60-100 μv, and in the subcortex the potential variation is from 20 to 60 μv. The frequency in the subcortex and in the archicortex is greater than in the neocortex. The EEG of sleeping animals shows typical high-voltage flow waves with rapid spindle-shaped oscillations.

Small doses of bulbocapnine (25-30 μg) have practically no influence on the EEG. Larger doses of 30-100 mg/kg cause a relative increase in the periods of activated electrical activity and reduce the unactivated period (Fig. 1). In certain animals paroxysmal highly synchronized charges occur. They were particularly noticeable when associated with highly synchronized discharges, and naturally they were much less well shown in the initial EEG.

The appearance in certain parts of the archicortex and in the medial thalamic nuclei of bursts of characteristic high-frequency spindles following regularly one after the other at intervals of about $1^1/2$ seconds was of special interest (Fig. 2). These spikes were best shown in the septal region, they were somewhat less marked in the hippocampus where they appeared less seldom; they also occurred from time to time in the medial thalamic nuclei. Unfor-

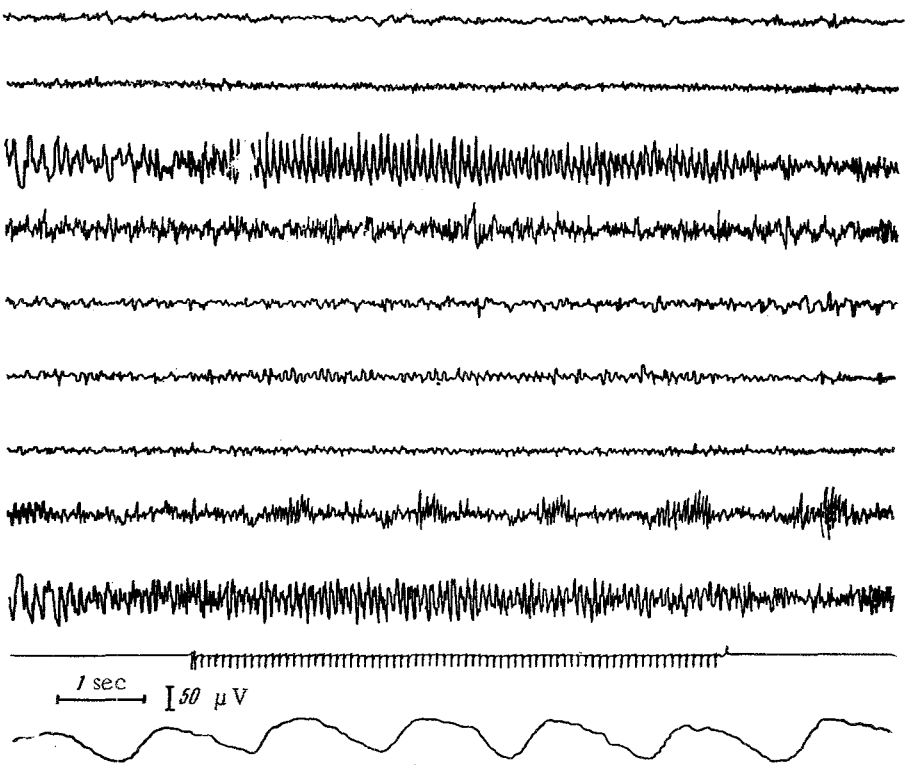

Fig. 4. Involvement of the specific projection areas and other cerebral structures. Indications as in Fig. 1.

tunately we were unable to establish any rule governing the appearance of these interesting spindles in the EEG: they were recorded both during deep stupor and catalepsy as well as at the onset and cessation of this state: in addition they occurred when the symptoms were not well shown. However we may note that very commonly these electrophysiological changes occurred in the structures mentioned at the time that principal cortical activity became desynchronized (Fig. 3), i.e. when some sort of orienting reaction or a reaction to an extremely strong stimulus was applied. We should note that a similar high-frequency spikes occur during the action of certain hallucinogenic drugs (LSD 25), nivaline and phenamine which potentiate the action of central mediators exert a similar effect.

Thus during the action of bulbocapnine changes in cerebral electrical activity may be observed in various cortical and subcortical structures. However it is not possible to determine the structure whose change in activity is first initiated by bulbocapnine. We may however note that in all structures the nature of the changes is the same, and the EEG shows enhanced "activation."

The reactive changes in the EEG in response to bulbocapnine show certain characteristic features. They appear for a long time during the arousal reaction, which reaction is extinguished only after a particular stimulus has been used a large number of times. The reaction in which the electrical activity takes up the rhythm of the stimulus may be observed in the EEG not only in the specific projection structures (for example the visual cortex during rhythmic photic stimulation), but also in the motor cortex and in the non-specific subcortical structures, as well as in the amygdala and hypothalamus (Fig. 4).

Besides the question of whether the reactivity of the brain is increased in bulbocapnine poisoning we have also to enquire whether the threshold of excitability to various stimuli not always noticed by the experimentor may be lowered. Thus it has been observed that isolated light flashes or the presentation of any stimulus may evoke in certain animals an electrophysiological response in the form of a highly synchronized charge, and we have found that these discharges could be recorded even when there was no external stimulus. It may be that during this period there was some interoceptive stimulus or else a "pseudostimulus" which was "sensed" by the animal in its pathological condition.

The results we have obtained indicate that the drug bulbocapnine which we have investigated possesses to a marked degree the property to induce a profound catalepsy and stupor in cats. The results of our study of the influence

of bulbocapnine on cerebral electrical activity indicates that this substance exerts an activating influence on cells of the central nervous system. Passouant [8] maintains that bulbocapnine reduces the excitability of various parts of the central nervous system, but this view does not seem to us to be well founded because Passouant determined excitability in terms of muscular contraction; however this method is not adequate under conditions of bulbocapnine poisoning. The fact that the changes in electrical activity are widespread and that no structure can be identified as initiating the change or being chiefly concerned in the change indicates that bulbocapnine acts on nerve cells at all levels in the central nervous system.

SUMMARY

Experiments were carried out on cats with electrodes implanted into the cortex and subcortex. A study was made of the effect produced by bulbocapnine on behavior and cerebral electrical activity. The motor effects included catalepsy and stupor, there were also sympathetic, parasympathetic, and emotional disturbances. The electrical changes occurred simultaneously in the cortex and the subcortex, and represented an activation. There was a marked increase in the cerebral responses to external stimuli, including rhythmic stimuli. We concluded that bulbocapnine exerts a central effect of a global nature and that both the sensory and motor elements of the cortex and subcortex are involved.

LITERATURE CITED

1. V. S. Deryabin, Zh. vyssh. nervn. deyat., No. 4 (1951), p. 469.
2. A. O. Dolin, Transactions at the combined session held at the 10th anniversary of the death of I. P. Pavlov, Moscow, (1948), p. 207.
3. A. O. Dolin, Zh. vyssh. nervn. deyat., No. 4, (1951), p. 485.
4. L. I. Kotlyarevskii, Zh. vyssh. nervn. deyat., No. 4, (1951), p. 579.
5. A. Boriani, Riv. Neurol., 19, (1949), p. 273.
6. I. Gadamer, Arch. Pharm. (Weinheim), Bd. 240 s. 19 (1902).
7. H. de Jong and H. Baruk, La catatonie experimentale par la bulbocapnine. Paris, (1931).
8. P. Passouant, Th. Passouant-Fontaine, and J. C. R. Cadilhac, Soc. Biol., 149, (1955), p. 2185.
9. F. Peters, Arch. exp. Path. Pharmak., Bd. 51, s. 130 (1904).
10. U. Z. Poppi, ges. Neurol. Psychiat., Bd. 154 s. 458 (1936).
11. G. Schaltenbrand and S. Cobb, Pflüg. Arch. ges. Physiol., Bd. 218, s. 475 (1928).

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