EFFECT OF NANOPHYNE, PACHYCARPINE, AND GANGLERON ON THE ACTIVATING AND CONVULSANT EFFECTS OF NICOTINE

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Reports in the literature [4, 23, 24, 25] and the results of our own investigations of phase changes in the electroencephalogram (EEG) caused by nicotine [7, 8] have made necessary the study of the neurochemical mechanisms lying at the basis of the convulsant and activating effects of this drug. A satisfactory way of investigating this problem appeared to be by studying the influence of nicotine-like cholinolytics on these effects. Gangleron and pachycarpine, with a central nicotinolytic action [1, 2, 3, 11, 13], and nanophyne, with a peripheral nicotine-like cholinolytic action [9, 10, 12], were used. The chemical structure of the last compound affords some evidence suggesting that it may be able to pass through the blood-brain barrier and to produce central effects.

EXPERIMENTAL METHOD

The electrical activity of the brain was investigated in 70 rabbits with an intact brain and in cats with trigeminal section of the brain stem. The technique of encephalography and of trigeminal section by mechanical and electrolytic methods has been described previously [7, 8]. The drugs for investigation were injected intravenously.

A

B

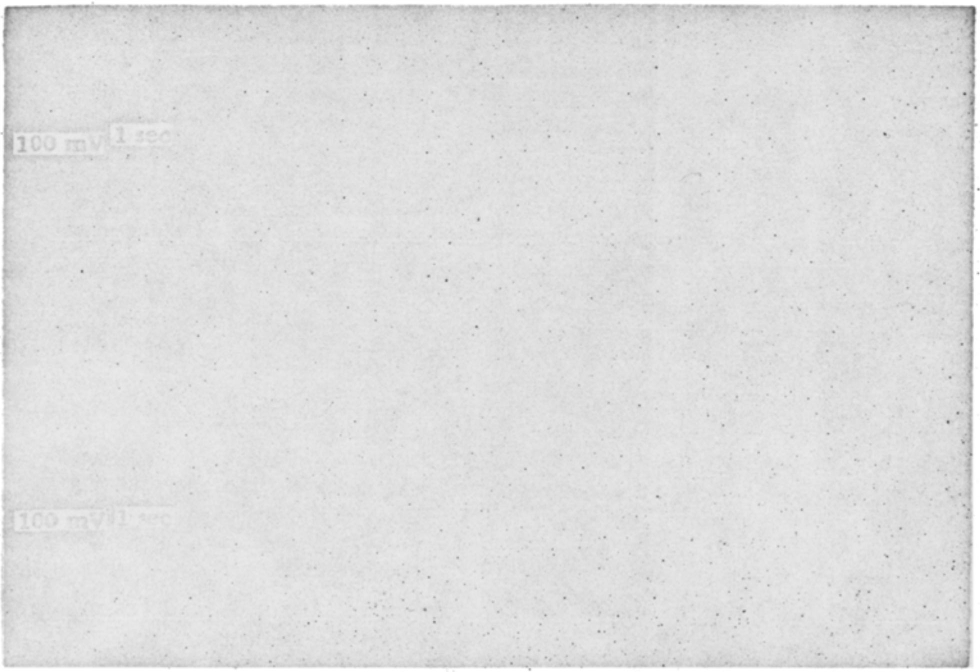

Fig. 1. Effect of nanophyne [illegible]. Significance of the curves (from above down): [illegible] and optic, and right sensorimotor areas of the rabbit's cortex; ECG; A) before injection; B) 5 min after injection of nanophyne in a dose of 9 mg/kg.

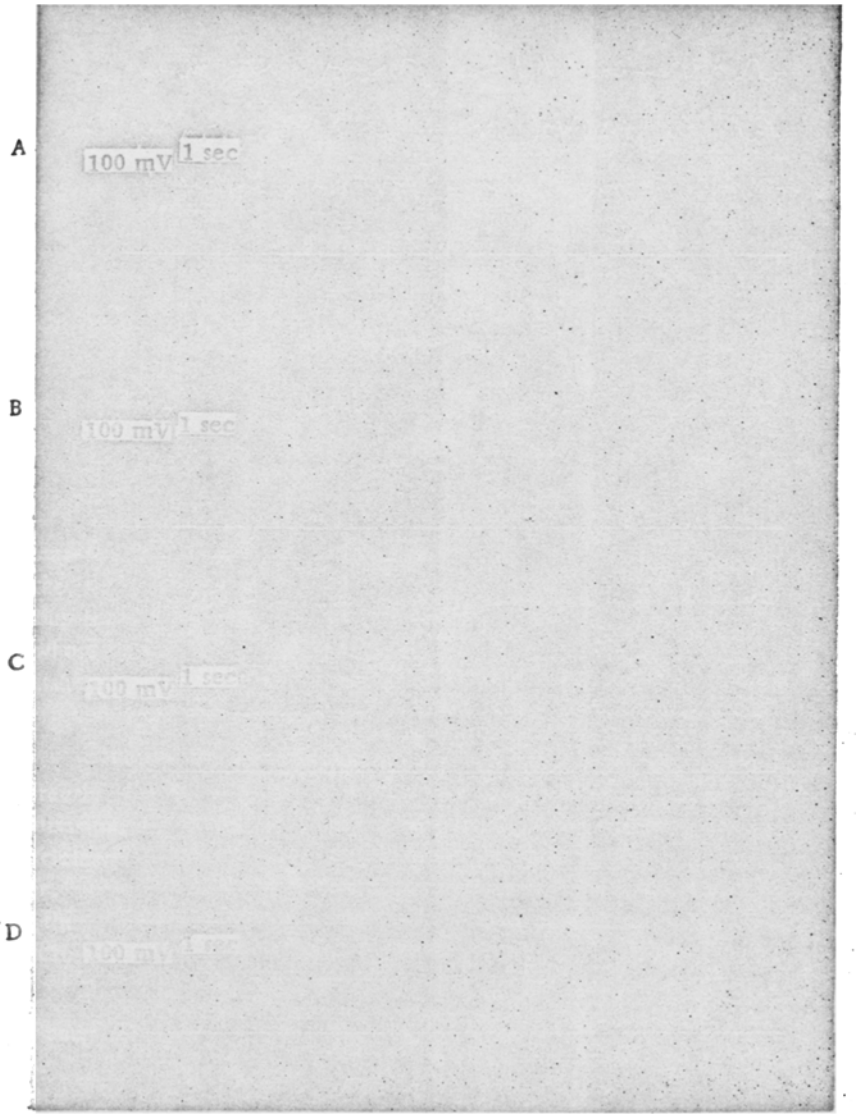

Fig. 2. Prevention of the convulsant effect of nicotine by gangleron. Significance of the curves (from above down) as in Fig. 1. A) Before injection; B) 14 min after injection of gangleron in a dose of 10 mg/kg; C) 20 sec after injection of nicotine in a dose of 1 mg/kg; D) 30 sec after a further injection of nicotine in a dose of 1 mg/kg.

EXPERIMENTAL RESULTS

The investigations showed that the changes in the EEG during the action of nanophyne, pachycarpine, and gangleron depended on their rate of injection. If the rate of injection was 2.5-3 mg/kg/min, gangleron in doses of up to 10 mg/kg had no effect on the EEG; in a few experiments a tendency towards activation was observed both in the cerebral cortex and in the mesencephalic reticular formation, the reticular nuclei, and the centrum medianum of the thalamus. If injected more rapidly (up to 10 mg/kg/min), slow waves appeared in the EEG of most animals in the first 5 min, with signs of depression of the electrical activity of the brain of varying degree, sometimes amounting to the complete absence of potentials. The same relationship between the recorded EEG pattern and the rate of injection and dose of the drug was observed also in the case of pachycarpine and nanophyne. When injected at a rate not causing depression of the bioelectrical activity of the brain, gangleron, pachycarpine and nanophyne had no effect on the degree and duration of the arousal reaction to application of an acoustic stimulus or to electrical stimulation of the sciatic nerve (Fig. 1).

After injection of gangleron and pachycarpine in doses of up to 10-20 mg/kg the characteristic activation pattern of trigeminal section also remained unchanged. Nanophyne, in doses of 10-15 mg/kg, caused isolated spindle-shaped waves to appear in the EEG.

These investigations showed that nicotine, in a dose of 1 mg/kg, which produces both a phase of activation and a phase of convulsive discharges in the EEG, when injected after gangleron (10 mg/kg) led to the appearance of activation only. No convulsive discharges developed in the EEG and outwardly the animals remained quiet. Nor did convulsive discharges develop in the EEG when larger doses of nicotine were given (up to a total of 3-5 mg/kg), but only a phase of activation was recorded (Fig. 2); neither clonic nor tonic convulsions were present. Preliminary control experiments revealed that repeated injections of nicotine give rise to a marked activation reaction. In cases when the first injection of nicotine (in doses of less than 0.5-1 mg/kg) gave an activation reaction only, after repeated injections a phase of convulsive discharges appeared in addition to the phase of activation.

Similar results were obtained in the experiments with nanophyne. The anticonvulsant effect of pachycarpine was weak. A preliminary injection of this drug in a dose of 10 mg/kg did not prevent the development of a phase of convulsive discharges in the EEG, accompanied by actual convulsions. When the dose of pachycarpine was increased to 30-40 mg/kg, the drug exhibited an anticonvulsant effect, but only in a small proportion of the animals. Larger doses were not tested, for they caused a marked disturbance of the animal's general condition, abnormalities of the ECG waves, disappearance of brain potentials, respiratory arrest, and death of the animal.

These investigations thus showed that the cholinolytics under test do not cause significant changes in the EEG if they are injected slowly enough. We know that the degree of the EEG changes, reflecting the severity of the disturbance of the cerebral circulation, is dependent on the rate of fall of the arterial pressure [19, 20]; when the arterial pressure falls to 25-30 mm the blood flow through the capillaries of the brain ceases [22]. This probably accounts for the appearance of slow waves and signs of depression during the action of gangleron [2], pachycarpine [9], and nanophyne.

The fact that the nicotine-like cholinolytics block only the convulsant action of nicotine and not its activating action suggests that these two effects of nicotine are based on different neurochemical mechanisms. Experimental evidence obtained in relation to the convulsant effect of nicotine fits in with the notion that this action is based on excitation of the nicotine-like cholinergic structures by the drug. However, the activating effect of nicotine can hardly be explained entirely by excitation of the central nicotine-like cholinergic structures. Proof of this is given by the fact that after repeated injections of nicotine (0.3-1.0 mg/kg) its ability to cause activation of the EGG persists. Meanwhile the convulsant effect of nicotine in relation both to motor activity [5, 14, 16, 23] and to changes in the EEG [18] does not develop after repeated injections of the drug.

Probably the nicotine-like cholinergic structures in general do not play the principal part in the activation reaction developing not only in response to pharmacological agents, but also in response to external stimuli of different character. The severe curtailment of the activating effect of nicotine by the preliminary injection of central muscarine-like cholinolytics and their ability to abolish existing nicotine activation[8] support the view that muscarine-like cholinergic structures play a part in this mechanism, probably at a higher level in the central nervous system. However, the principal argument against this view is the fact that against the background of an established action of the muscarine-like cholinolytics, nicotine still causes transient activation. This suggests either than nicotine possesses a very strong activating effect, exceeding the blocking action of the muscarine-like cholinolytics, or that excitation of some other chemically sensitive elements occurs.

SUMMARY

The effect of nanophyne, gangleron, and pachycarpine on the background bioelectric activity, and on the activating and convulsant effects of nicotine were investigated in experiments on 70 rabbits with the brain intact and on cats with trigeminal section of the brain stem. The degree of the EEG changes depended on the rate of administration of the preparations.

With sufficiently slow administration (about 3 mg/kg/min) there was no change in the character of the background activity. In doses of 5-10 mg/kg gangleron and nanophyne possessed a marked central nicotinolytic effect, but it was manifested only in the blocking of the convulsive effect of nicotine; the activation reaction caused by nicotine was retained. These drugs also did not block the activation reaction caused by the acoustic stimulation or electric stimulation of the sciatic nerve. The anticonvulsant effect of pachycarpine proved to be weak and inconstant. The data obtained suggest that different neurochemical mechanisms underlie the convulsive and activating effects of nicotine.

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