AN ELECTROENCEPHALOGRAPHIC ANALYSIS OF THE DISTINCTIVE FEATURES OF THE ACTION OF AMINAZINE (CHLORPROMAZINE) ON DOGS OF DIFFERENT AGES

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Investigations in the Laboratory of the Physiology and Pathology of Aging dealing with the electroencephalographic analysis of the distinctive features of natural and narcotic sleep in dogs of different ages have shown that in young puppies the differences in the electroencephalogram (EEG) of the cerebral cortex when awake and asleep are absent. It was also shown that administration of narcotic doses of sodium amytal to puppies ages from 1 to 18 days produces none of the slow, high amplitude potentials typical of this state in adult animals [3, 4, 7]. These findings prompted us to ascertain whether aminazine possess neuroplegic properties in the course of its action on animals of different ages.

Phenothiazine derivatives (largactil, chlorpromazine, megaphen, R.P. 4560) have now been widely introduced into pediatric practice [14, 15, 19-21 and others]. Whereas the enormous spread of the use of neuroplegic drugs in various diseases of adults is based on a wealth of experimental research [1, 6, 8, 12, 17, 18 and others], the use of these drugs in children is purely empirical. No reports of experimental work on the study of the characteristics and mechanisms of action of the phenothiazine derivatives as related to age are to be found in the literature.

In the present investigation we made an electroencephalographic analysis of the action of aminazine (a drug synthesized at the All-Union Research Chemopharmaceutical Institute and the analog of largactil, chlorpromazine and megaphen) on the functional state of the brain in puppies ages from 1 day to 3 months in comparison with its action on adult dogs.

EXPERIMENTAL METHOD

Experiments were carried out on untied puppies kept on a soft litter in a box, which restricted their mobility but did not prevent them from adopting a free position. The EEG was recorded with bipolar leads, using needle electrodes. The parietal lead was the one mainly used, with an interpolar distance of 1-1.2 cm. The recording was made by means of a two-channel electroencephalograph (oscillograph) with an ink tracing. The transmission band was from 1 to 100 cps. Amplification – 1 cm – 50 μ v.

An aqueous solution of aminazine was injected intramuscularly in doses of 4 to 200 mg/kg. The doses mainly used were from 4 to 20 mg/kg, lying within the limits of the doses tolerated by dogs [8, 11].

Altogether 5 adult dogs and 52 puppies, ages from 1 day to 3 months, were investigated.

EXPERIMENTAL RESULTS

In the adult dogs, injection of aminazine in doses of 4-5 mg/kg caused after 20-30 minutes a tranquil and drowsy state, with a lowering of muscle tone. In the EEG a change was observed from the so-called desynchronized rhythm (35-60/ sec; Fig. 1, a) to a synchronized rhythm of alpha type, with the appearance of spikes (see Fig. 1,b). After injection of aminazine in doses of 15-20 mg/kg, after only 10 minutes slow waves of high amplitude appeared (60-75 μv), of the theta type — 4-5/sec (see Fig. 1, c). These waves were dominant in the EEG of the adult dog for the 2-4 hours after injection of aminazine, when the dog was in a state of cataplexy and light sleep (see Fig. 1, d, e, f, g, h). The frequency of the oscillations then began to increase to 6-7/sec and above, and the amplitude to diminish (see Fig. 1, i, j, k, l).

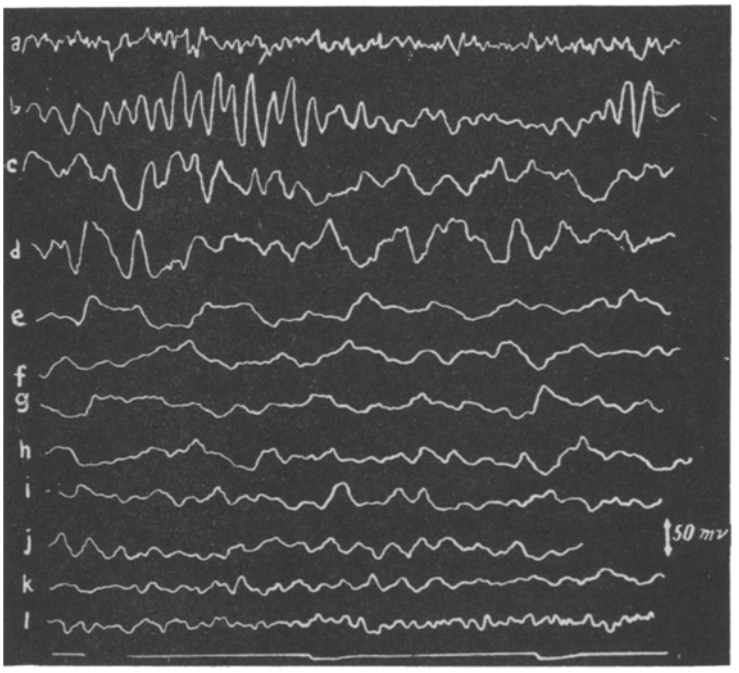

Fig. 1. Electroencephalogram of an adult dog. a) Original background; b) 10 minutes after injection of aminazine in a dose of 5 mg/kg; c) 20 minutes after injection of aminazine in a dose of 20 mg/kg; d) 30 minutes after second injection; e) after 1 hour; f) after 1 hour 30 minutes; g) after 1 hour 50 minutes; h) after 2 hours; i) after 2 hours 10 minutes; j) after 2 hours 30 minutes; k) after 3 hours; l) after 3 hours 20 minutes. Bottom line) time in seconds.

Tactile or painful stimuli or inhalation of ether during the time of action of the aminazine led to awakening of the animal, moaning and the appearance of a desynchronized rhythm on the EEG, disappearing on cessation of the stimulation.

The results which we obtained in experiments on adult dogs were in full agreement with the electroencephalographic characteristics of the action of phenothiazine derivatives on adult animals as described in the literature, mainly on rabbits [9, 10, 16, 23].

The predominance of slow waves in the EEG of the adult animals during the action of aminazine is, in the modern view, the result of blockade of the nonspecific nuclei of the ascending part of the reticular system. According to the accepted view of our laboratory, these nuclei play in relation to the cells of the cerebral cortex the role of an intermediate link, in which during natural and narcotic sleep a second catelectronic phase of the parabiotic process develops, in consequence of which a positive electric potential and associated slow "sleep" potentials develop conjointly in the cerebral cortex itself [2-4].

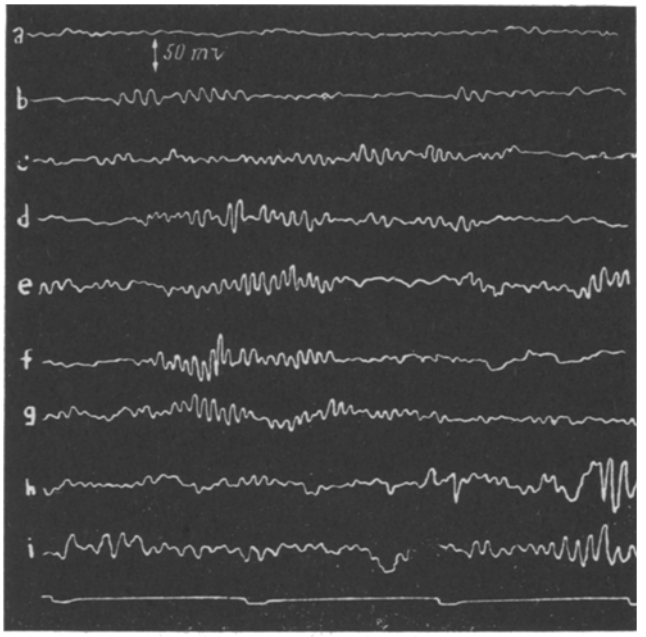

Fig. 2. Electroencephalogram of a 6-day old puppy. a,b) Initial background; c) 10 minutes after injection of aminazine in a dose of 4 mg/kg; d) 20 minutes after injection of aminazine in a dose of 20 mg/kg; e) 20 minutes after the second injection; f) after 1 hour; g) after 2 hours; h) after 7 hours; i) after 24 hours. Bottom line) time in seconds.

In blind puppies ages from 1 to 10 days, after injection of aminazine in doses of 4 to 20 mg/kg the changes in the EEG differed very sharply from those which we observed in the adult animals.

As shown in our laboratory, the main electrical activity in puppies ages from 1 to 18 days in a waking condition is waves with an average frequency of 10-14/sec (10-20 μv) with a lower limit of 6-8 and an upper limit of 14-16/sec. In contrast to this main rhythm, the slow waves with a frequency of 3-4/sec are inconstant and are characterized by a low amplitude (10-12 μv). These oscillations are episodic, and occur for a short time both during sleep and when awake.

Injection of aminazine in a dose of 4-5 mg/kg to young puppies (1-10 days) led to a fall of 2-3° in the body temperature and a lowering of muscle tone. From 5 to 10 minutes after the injection, an increase in the frequency of the waves in the EEG to 19/sec was observed, with an increase in the amplitude to 30-35 μv (Fig. 2,c). The electrical activity rose periodically, in bursts, in the intervals between which were observed slower rhythms, typical of the original EEG. Injection of aminazine in doses of 10-20 mg/kg [2] caused a still more pronounced activation of the EEG of the blind puppies; this took the form of a periodic quickening of the main rhythm, to as much as 20-21/sec, with an increase in the amplitude to 65-100 μv (see Fig. 2, f, g).

In Fig. 2 is shown the EEG of a 6-day-old puppy before and at definite intervals of time after the injection of aminazine in doses of 4 and 20 mg/kg.

Three hours after the injection of aminazine the bursts of increased activity in the EEG became less pronounced, although they could still be observed for several hours (see Fig. 2, i). The increased activity in the EEG corresponded to a state of slight restlessness in the puppy, as shown by moaning and even by crying out.

After injection of very large doses of aminazine (50-100-150-200 mg/kg) to puppies ages from 1 to 10 days, after an initial period of activation of the EEG there followed a decrease in the amplitude and frequency

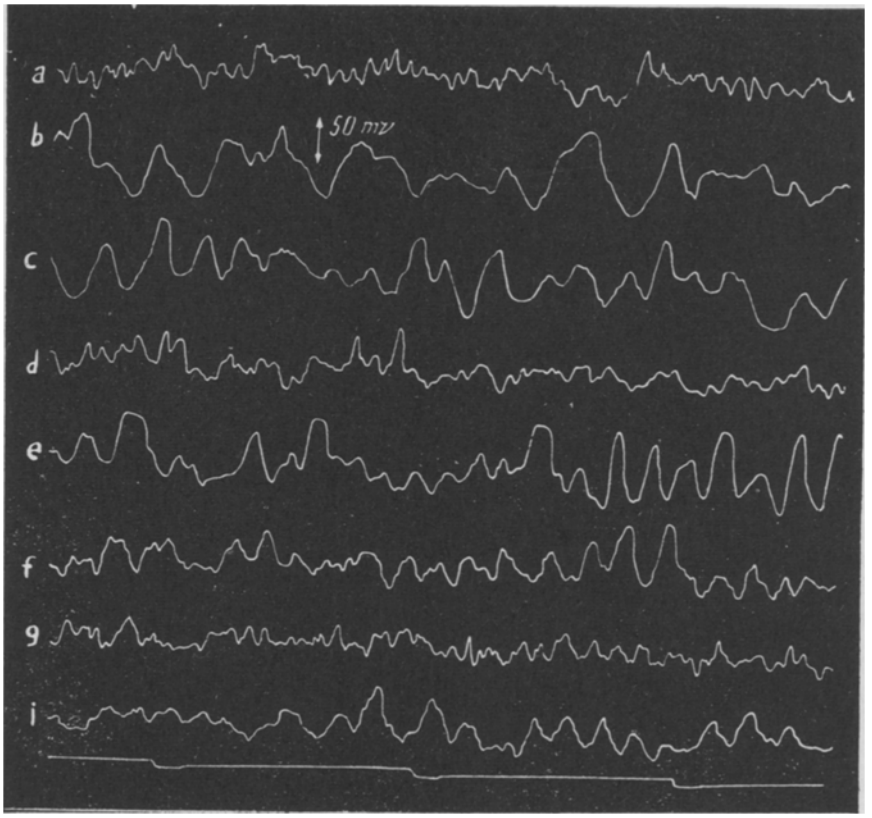

Fig. 3. Electroencephalogram of a 20-day old puppy. a) Initial background; b) 20 minutes after injection of aminazine in a dose of 20 mg/kg; c) after 50 minutes; d) after 55 minutes — tactile stimulation; e) 2 hours after injection; f) after 3 hours; g) after 4 hours; h) after 5 hours. Bottom line) time in seconds.

of the main electrical activity. Even with these very large doses, however, the appearance of slow, high-amplitude potentials, typical of adult dogs, was not observed in the young puppies.

In the period of maturity of the puppies, at the age of 10-12 days, the injection of aminazine in doses of 5-20 mg/kg no longer caused the increase in the electrical activity of the brain described in the case of the blind animals; this activity was fundamentally unchanged and remained at the level of the original characteristics or was even slightly lowered. In some cases (in 5 experiments of 12), in contrast to the blind animals, the appearance of periods of slow waves with a frequency of 3-4/sec was observed in the puppies of this age. In contrast to the "sleep" potentials of adult dogs, however, the amplitude of the slow waves in the EEG of the puppies ages 10-12 days was far lower (25-40 μv). The onset of these waves was of an episodic character, in contrast to those in adult dogs, and did not determine the character of the EEG after injection of aminazine; the dominant rhythms in the EEG were those typical of the initial background at this age. As was pointed out above, slow waves (with a frequency of 3-4/sec) of low amplitude may appear episodically in young puppies in a waking condition also.

According to findings in our laboratory, the main electrical activity in puppies, starting at the age of 18-20 days, is characterized by a rather higher frequency — 16-18/sec — with an upper limit of 20-22/sec. At this age for the first time, slow waves of the delta type (3-4/sec) with an amplitude of 75-100 μv appear 20-30 minutes after injection of aminazine in doses of 5-20 mg/kg (Fig. 3, b). In Fig. 3 are shown the changes in the electrical activity of the cerebral cortex of a puppy age 20 days during the 5 hours after injection of aminazine in a dose of 20 mg/kg. From 40 to 50 minutes after its administration to 18-to 20-day-old puppies the rhythm of the slow potentials was slightly increased in frequency (to 5-6/sec), and their amplitude fell slightly to 50-75 μv (Fig. 3, c).

It can be seen from Fig. 3 that in response to tactile stimulation a more frequent rhythm (16-18/sec) appeared temporarily, characteristic of the original condition, or an even more frequeny rhythm was observed to be superimposed on the slow waves, which at this time were of diminished amplitude. From 2 to 3 hours after the injection the frequency of the slow waves increased to 6-8/sec, with a gradual decrease in their amplitude (see Fig. 3, e, f). Fig. 3, g showed the quickening of the waves in the EEG during the puppy's cry. Five hours after the injection of aminazine, slow waves still predominated (5-6/sec), but their amplitude was considerably decreased (Fig. 3, h).

The changes described in the 18-to 20-day-old puppies were also characteristic of the action of aminazine in puppies up to the age of $1\frac{1}{2}$ months. Starting with 3rd-4th month of the animals, the action of aminazine on the EEG of the cerebral cortex did not differ from the characteristics which we have described for the adult dogs.

It may be concluded from the results obtained that the changes in the EEG resulting from the action of aminazine on young puppies (up to 18 days old) differ from those changes which are typical of puppies more than 18 days old or of adult dogs. It is a fact of fundamental importance that not only are the slow "sleep" potentials absent in young puppies, but there is even an increase in the frequency and amplitude characteristics of the EEG in puppies age up to 10 days. This "activation" of the EEG differs from that designated by several authors by the same term, referring to the change in the EEG of the adult animal in response to the action of phenothiazine derivatives [13, 16, 22 and others].

This particular fact, taken in conjunction with I. I. Gokhblit's [7] findings that there is no difference between the electrical activity of the cerebral cortex in young puppies when awake and asleep, confirms the accepted view of our laboratory of the absence of functional, and perhaps even of structural maturation of the corresponding nonspecific nuclei of the ascending divisions of the reticular system.

Although it has not been possible at this stage to give an interpretation of the increase in the frequency and amplitude of the EEG waves in blind puppies after injection of aminazine, we are, nevertheless, justified in concluding that the results of the electroencephalographic analysis do not permit us to categorize aminazine as a drug possessing typical neuroplegic or transquilizing properties when used in a young animal or child. The neuroplegic properties of aminazine become apparent only when the drug is administered to puppies over 18-20 days old.

SUMMARY

Changes in the EEG caused by the action of aminazine (phenothiazine derivative) on puppies, ages from 1 to 18 days, differ from those typical for older puppies and adult dogs. Not only slow "slumber" potentials are absent in the puppies under 18 days of age, but there is also a certain increase of the frequency-amplitude characteristics. This fact confirms the view accepted in Professor I. A. Arshavskii's laboratory on the absence of the functional maturation of the corresponding nuclei in the ascending portion of the reticular system in young animals. The neuroplegic properties of aminazine are manifested in puppies only by the 18th–20th day of life.

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