THE MECHANISM OF PROTRACTED COLLAPSE IN YOUNG ANIMALS DUE TO THE ACTION OF BACTERIAL TOXINS

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Research in our laboratory has shown that different pathogenic agents (bacterial toxins, pharmacological substances in suitable doses) cause a state of protracted collapse in young animals [5, 7]. Several workers have shown that this type of reaction in young animals is associated with the special features of tissue metabolism which permit the utilization of anaerobic energy in a state of collapse [6, 9]. This usually accounts for the ability of young animals to survive for a long time in conditions of severe anoxia. At the same time it has been shown in our laboratory that during anoxia, protracted collapse can develop in young rabbits and kittens only when the body temperature is constantly falling; prevention of cooling very rapidly leads to death with signs of rapid collapse of the type characteristic of adult animals [1, 3].

The aim of the present investigation was to assess the importance of a falling body temperature as a factor permitting the prolonged survival of young puppies subjected to the action of bacterial toxins, and to study the changes in the condition of certain nerve centers.

EXPERIMENTAL METHOD

Experiments were performed on puppies ages from 1 day to 3 months. The animals were given an intravenous injection of a lethal dose of staphylococcal or dysentery toxin causing death after 4-12 hours. For this purpose we used liquid staphylococcal toxin in a dose of 0.2-0.5 ml/kg body weight and complete Hiss-Flexner antigen in a dose of 5-7 mg/kg body weight. In order to determine the state of the cerebral cortex, the electroencephalogram (EEG) was recorded. Bipolar leads were taken, using needle electrodes, which were inserted into the bones of the skull at the site of projection of the frontal or parietal lobe. In the majority of experiments the animal's head was firmly fixed in order to prevent artefacts. In addition, throughout the experiment, recordings were made of the electrocardiogram, the respiration and the body temperature. In a special series of experiments the animals were placed in an incubator with an air temperature of 30-31°. Altogether 78 experiments were performed.

EXPERIMENTAL RESULTS

Injection of lethal doses of staphylococcal or dysentery toxin to puppies ages $1\frac{1}{2}$-3 months caused the reaction already described above, with a four-phase change in the rhythm of the heart's contractions. Workers in our labatory [2, 5] have shown that the first phase, appearing soon after injection of the toxin, when the cardiac rhythm became slower on account of the increased tone of the center of vagus innervation of the heart. The second phase – a quickening of the activity of the heart – was due to a fall in the tone of the vagus. Later, during the development of a terminal state, a second increase arose in the tone of the center of vagus innervation of the heart; this was expressed by the phenomenon of syncope with subsequent change of the activity of the heart to an

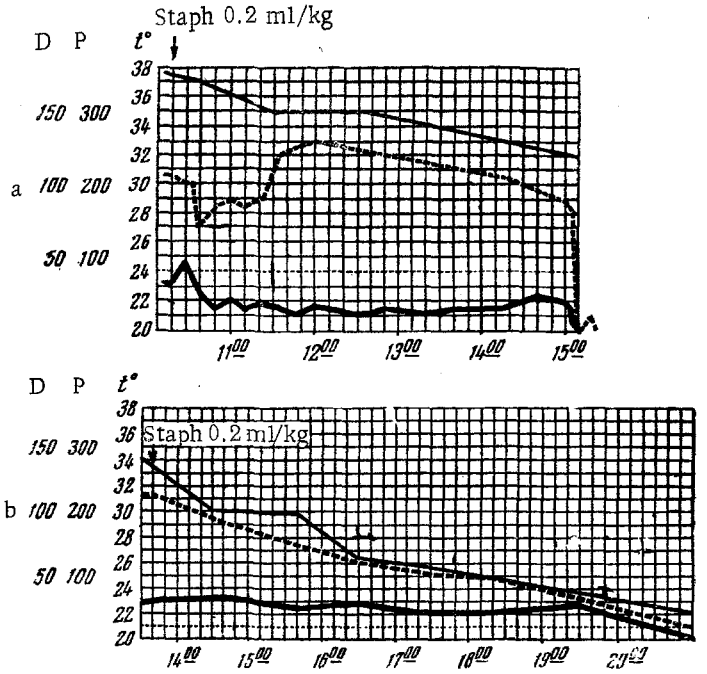

Fig. 1. The course of staphylococcal toxemia. a) In a puppy age 1 month 20 days; b) in a puppy age 7 days. Along the vertical axis – rectal temperature; P) number of contractions per minute of the heart; D) respiration rate. Along the horizontal axis – time in hours. ↓) Time of injection of toxin.

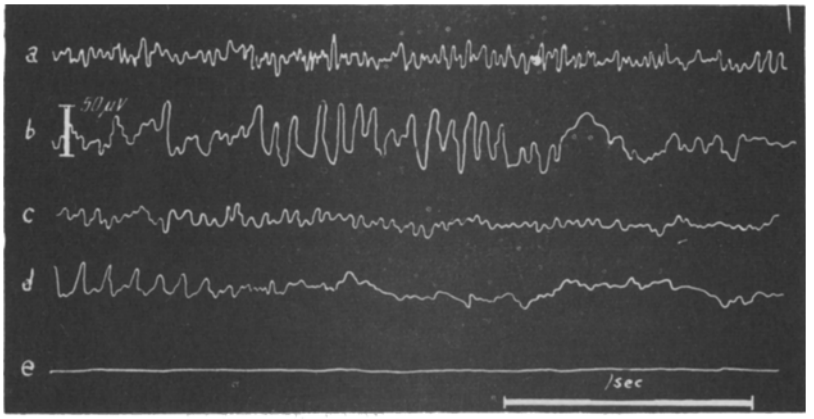

Fig. 2. Changes in the EEG (frontal lead) in a puppy age 2 months injected with staphylococcal toxin. a) Recording before injection of toxin; b) in the phase of the first slowing of the heart's contractions; c) in the phase of quickening of the heart's contractions; d) 5 minutes before cardiac syncope; e) during cardiac and respiratory syncope.

Aschoff-Tawara rhythm. This phase coincided with phenomena of syncope in the respiratory center also. Next followed the fourth phase – the change of the heart to an automatic rhythm and, possibly, to fibrillation. In this last phase terminal inspirations were observed at the same time. The last two phases, beginning with cardiac and respiratory syncope, lasted on the average 5-8 minutes, after which death ensued. These two phases were also characterized by what in adult dogs would in similar conditions be called collapse. Under these circumstances in adult dogs the body temperature, if lowered at all, does not fall by more than 1-3°. In puppies ages $1\frac{1}{2}$-2 months it may fall by 3-5° (Fig. 1).

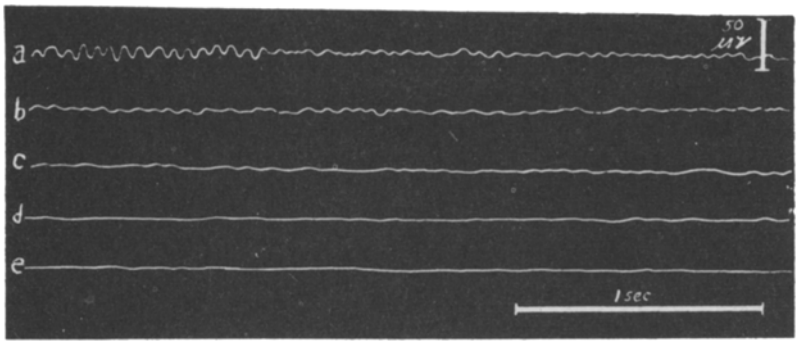

Fig. 3. Changes in the EEG in a puppy age 7 days (frontal lead) injected with staphylococcal toxin. a) Recording before injection of toxin; b) c, d) recordings made every 35-40 minutes; e) recording made 3 hours before cessation of breathing.

In experiments on puppies ages 1 to 14-15 days, with an ordinary environmental temperature (18-20°), injection of a lethal dose of bacterial toxins caused death which ensued after prolonged collapse; this was characterized by a gradual slowing of the rhythm of the cardiac contractions and the respiration, and a fall in the body temperature to the level of that of the surroundings (see Fig. 1).

From comparison of the results obtained it can be seen that distinctive features of age were manifested primarily by the fact that the animals in the first days of life did not show the phases of changes in cardiac activity typical of puppies over $1\frac{1}{2}$ months old. A further characteristic feature shown by the young animals was a considerable fall of the body temperature. Comparison of the changes in the EEG observed under these circumstances showed that in puppies over $1\frac{1}{2}$-2 months old, the development of toxic manifestations was accompanied by phasic changes in the electrical activity of the cerebral cortex (Fig. 2).

Cessation of the "spontaneous" electrical activity of the cerebral cortex in the terminal state in animals of this age group took place almost simultaneously with the appearance of cardiac and respiratory syncope.

In puppies during the first days of life (not more than 16-18 days old), protracted collapse developing after the injection of bacterial toxins was characterized by a gradual fall in the activity of the EEG, mainly of its amplitude, as far as complete disappearance of the rhythmic activity during the 3-5 hours before cessation of respiration and activity of the heart (Fig. 3).

In the performance of experiments with acute anoxia we found that the course of protracted collapse in young animals depended on the temperature of the environment. Protracted collapse was possible only when the environmental temperature was relatively low (not above 18-20°), at which the animal's own body temperature fell comparatively quickly. By analogy with the anoxia experiments it was decided to ascertain to what extent the fall in the body temperature was a factor influencing the duration of the collapse after injection of toxin. For this purpose a series of experiments was carried out on puppies ages up to 10 days, at an environmental temperature of 30-31°, preventing cooling of the animal. Staphylococcal toxin was injected intravenously in the same dose as in the puppies during the experiments at room temperature. In these conditions death of the animal took place much more quickly (after $1\frac{1}{2}$-3 hours) with none of the typical signs of protracted collapse as described above. Phasic changes were observed in the activity of the heart and the EEG, but these were different from those in adult animals. The duration of the collapse was greatly shortened – the pattern of death was closer to that observed in adult animals. In these cases too, however, the cessation of electrical activity of the cerebral cortex arose long before the arrest of respiration and of the activity of the heart ($\frac{1}{2}$-$1\frac{1}{2}$ hours).

The experiments showed that protracted collapse in response to the action of bacterial toxins on puppies in the first days of life was only produced in conditions when it was possible for the body temperature of the animal to fall. The fall in the body temperature to the level of the environment temperature, and the disappearance of the EEG rhythms long before the cessation of respiration and of activity of the heart was evidence that in young animals the resistance of the diencephalic and cortical levels of the central nervous system is considerably below that of the bulbar and spinal levels.

What determines the possibility of long survival in a state of collapse when the body temperature is lowered? In order to eluidate this problem we carried out the following series of experiments. If a puppy, already in a state of collapse with a low body temperature, was carefully warmed, because of the increased body temperature a considerable quickening of the rhythm of contraction of the heart and of respiration could be observed. The animal quickly died from overheating, although a temperature much lower than normal, e,g., 33°, 27°, 23° and so on, depending on the depth of the collapse, determined by the degree of damage done by the toxin to the nerve centers.

As numerous observations in our laboratory haveshown, the normal body temperature of the puppies before puberty is 35-36°. On increasing the environmental and the body temperatures, the puppies die from overheating when their body temperature reaches 41-43°; death ensues rapidly, with no signs of protracted collapse [4]. The temperature at which the animals die from overheating should be referred to as limiting or critical. During overheating the cortical level is excluded much earlier than the cessation of the activity of the respiratory center, judging by the disappearance of the EEG, so that it can be accepted that at the critical temperature, death ensues as a result of the cessation of the function of the bulbar level, which in this case shows the greatest resistance.

The observations described above become understandable when it is remembered that, if we postulate that as a result of the action of bacterial toxins, the critical temperature and probably also the optimum temperature zone are shifted towards lower levels, more or less severely depending on the degree of current damage and the resistance of the nerve centers. The rate of shift of the critical temperature in the conditions of our experiments varied from fractions to a few degrees per hour. The inverse value of the rate of shift in these cases is a measure of the resistance of the nerve centers, their accommodating resistance to the damaging influence of the bacterial toxins. It must be pointed out that a fall in the critical temperature during different forms of alteration (the action of narcotics, oxygen lack, mechanical injury and so on) has been shown in many types of biological object – unicellular protozoa, isolated organs and so on [8]. In our experiments the same relationship held good, but was considerably complicated by the fact that we were dealing here with specific reactions of an intact animal.

It must, therefore, be accepted that prolonged survival in a state of protracted collapse is only possible if the intensity of fall of the animal's body temperature is not less than the rate of shift of the critical temperature. The rapid death of the animal without signs of protracted collapse in experiments in which cooling was prevented or during warming could be explained as death resulting from equilibrium at a lower level of the body temperature than the critical temperature.

The findings obtained compel us to turn once again to the question of mechanisms of resistance to the action of bacterial toxins as it depends on age. In our laboratory we associate the idea of resistance with the ability of the animal to bring about an integrated series of adaptive reactions, thanks to which the animal maintains the constancy of its internal environment, i.e., its homeostasis, under the new conditions. As the analysis shows, young animals are not yet able to bring about the complete series of reactions necessary for maintenance of homeostasis. We regard protracted collapse as an expression of departure from adaptation, but one which permits the young animal to survive for a long time in spite of the low resistance of its nerve centers.

Prolonged survival during protracted collapse in young animals is possible by virtue of the fact that the function of the centers of the bulbar and spinal levels is still possible after the activity of the cortex and adjacent subcortex has been excluded. In the process of ontogenesis, starting at a definite stage (from 16-20 days) in consequence of some degree of equalization of the lability and resistance of the different levels of the central nervous system, a closer functional union of these levels takes place. At this time the animal acquires the ability to produce adaptive reactions to agents altering the environment, thereby enabling the state of homeostasis to be maintained, although under these circumstances the power of transformation into a state of protracted collapse is lost.

SUMMARY

The reactions of young puppies (ages from 1 to 18 days) and of the older ones (ages from 1.5 to 3 months) to the action of lethal doses of staphylococcus and the dysentery toxins were analyzed on the basis of EEG, EKG respiration frequency and body temperature studies. In three month puppies a rapidly developing (within 5-8 minutes) collapse is followed by death. This collapse is characterized by an almost simultaneous disappearance of the EEG rhythms, respiratory center activity and that of the heart, as well as by an insignificant reduction of the body temperature (by 2-3°C). In case of young puppies death is preceded by prolonged collapse (lasting several hours).

In young animals the latter is characterized by a gradual decrease of the body temperature to the environment level with the electric activity of the brain cortex disappearing 3-5 hours previous to the death of the animal. When the body temperature is prevented from dropping, the period of protracted collapse isdecreased sharply. The above observations lead to the following explanation of this fact: in a protracted collapse of young puppies the liminal (critical) temperature at which the animal dies is decreased as a result of alteration of the nervous centers by bacterial toxins.

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