IMPORTANCE OF THE ANABOLIC PHASE OF THE REACTION IN MAINTENANCE OF HOMEOSTASIS IN DOGS OF DIFFERENT AGES WITH STAPHYLOCOCCAL POISONING

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A series of investigations conducted in our laboratory showed that dogs and puppies over 2-2½ months old, when exposed to various stress-producing stimuli and, in particular, in bacterial poisoning always respond initially with an anabolic (bradycardic) phase, and only after this with a catabolic (tachycardiac) phase. The important adaptive significance of the initial bradycardia was demonstrated, and its nature was shown to be cholinergic. Its severity determines the duration of the maintenance of homeostasis in the second tachycardiac phase, and also the more or less rapid onset of collapse and death of the animal [1,3,4,17,18]. In a previous communication we gave details of the level of oxygen consumption, which also confirm the anabolic nature of the first phase of the reaction during staphylococcal poisoning [20].

The object of the present study was to investigate the possibility of prolonging the bradycardic phase during staphylococcal poisoning with the aid of a parasympatheticomimetic agent such as morphine, which has the property of depressing metabolism [12,15] and which possesses anticholinesterase activity [13,14].

There are several reports in the literature of the beneficial action of morphine and other narcotics on the course of bacterial poisoning and, in particular, of staphylococcal poisoning, as revealed by changes in higher nervous activity [6,7,8]. The object of these experiments with morphine was to determine the significance of the increase in tone of the vagal innervation of the heart as a factor increasing its potential lability and enabling its resistance to staphylococcal poisoning to be determined. We were also interested in the importance of prolonged maintenance of the synchronized electrical activity characteristic of the action of morphine as an essential factor in the anabolic pattern of the initial bradycardic phase in staphylococcal poisoning.

METHODS

Experiments were conducted on dogs of two age groups: puppies aged between 1 and 16 days (1st group) and puppies over the age of 2-2½ months and adult dogs (2nd group). In different series of experiments staphylococcal toxin (IEM, batch No. 196) was injected subcutaneously and intravenously in doses of between 0.5 and 1.5 ml/kg. The ECG was recorded in lead 2, together with respiration and the EEG, on a four-channel electroencephalograph. Needle electrodes were used (bipolar leads), and were inserted into the cranial bones at the point of projection of the sensorimotor area of the brain. Respiration was recorded by means of an electrolytic pick-up. The changes in body temperature were recorded. Each subgroup contained equal numbers of experimental and control dogs and puppies, which received the same dose of toxin. Between 30 and 40 min before injection of the toxin, the experimental animals received a subcutaneous injection of morphine in a dose of 10 mg/kg.

RESULTS

The absolute lethal dose of staphylococcal toxin when injected intravenously into the animals of the 1st and 2nd groups was 0.5 ml/kg. In most cases, however, the adult dogs and puppies more than 2-2½ months old died

Duration of Anabolic Phase and Duration of Survival in Staphylococcal Poisoning

Subgroup of animals	Dose of staphylococcal toxin (ml/kg)	Control (without injections of morphine)			Experiment (preliminary injection of morphine)		
		No. of animals	Duration of anabolic phase	Duration of survival	No. of animals	Duration of anabolic phase	Duration of survival
A	0.5	3	1 h 25 min-2 h	16 - 18 h	3	$4^1/_2$ - 6 h	Survived
B	0.75	3	50-55 min	$3^1/_2$ - 6 h	3	$4^1/_2$ - 5 h	18-20 h (death)
C	1	4	20-25 min	1 h 25 min -2 h 45 min	4	$3^1/_2$-$4^1/_2$ h	4 h 35 min-18 h

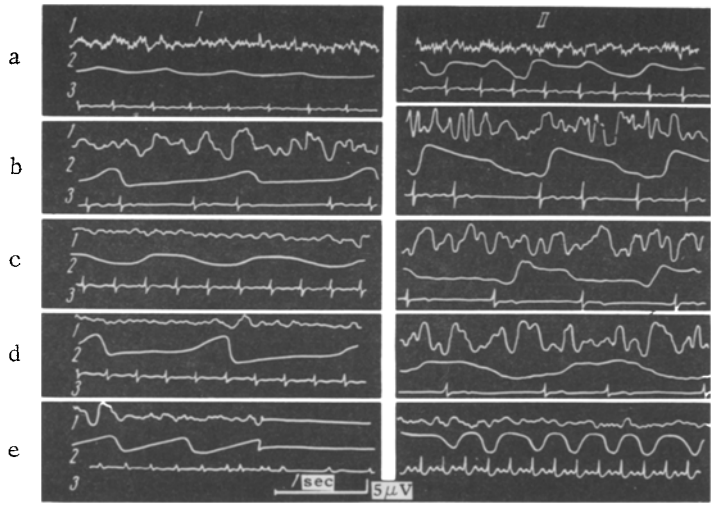

Fig. 1. EEG (1), respiration (2) and ECG (3) of adult dogs. I) control dog after injection of staphylococcal toxin in a dose of 0.75 ml/kg; II) experimental dog after injection of morphine (10 mg/kg) and staphylococcal toxin (0.75 ml/kg); a) initial background; b) 20 min after injection of toxin; c) 1 h; d) 4 h; e) $4\frac{1}{2}$ h after injection.

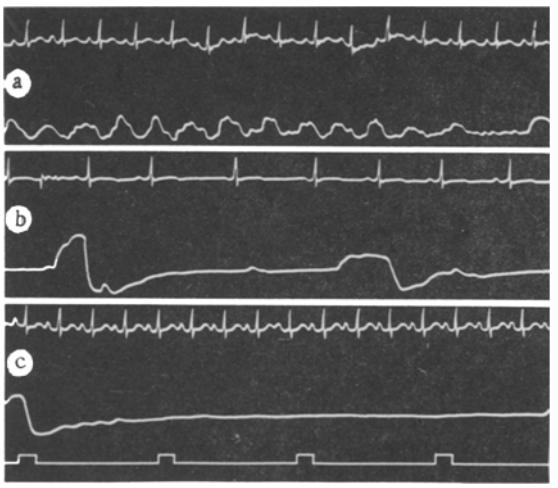

Fig. 2. ECG and respiration in a 5-day old puppy. a) before injection of morphine; b) 40 min after subcutaneous injection of morphine in a dose of 10 mg/kg; c) after injection of atropine in a dose of 0.2 mg/kg. Bottom line—time (in sec).

from this dose 16-18 h after administration, compared with $1\frac{1}{2}$-3 h after administration for the younger puppies. A dose of 0.2 ml/kg was the maximal tolerated dose for both groups of animals.

Intravenous injection of staphylococcal toxin in lethal doses caused the development of a transient collapse immediately after the bradycardic and tachycardiac phases. This collapse occurred in two phases: a phase of syncope and vagus escape and a phase of fibrillation, or a change to automatic rhythm. With an increase in the dose of toxin, the bradycardic phase was shortened, the duration of the tachycardiac phase was reduced, and collapse and death of the animals supervened sooner. On this account the dogs and puppies of the 2nd group (20 animals) were divided into 3 subgroups—A, B, and C—depending on the dose of toxin injected intravenously into each animal (see table).

The results given in the table show that in the control animals, as the dose of toxin was increased, the duration of the anabolic bradycardic phase was reduced and the period of survival was shortened. In the experimental animals receiving a preliminary injection of morphine, a sharp rise in the duration of the bradycardic phase and in the survival period was observed after injection of all the tested doses of toxin. The absolute lethal dose of the animals receiving morphine was 0.75 ml/kg of toxin, and of the control animals—0.5 ml/kg of toxin.

It can be see from Fig. 1 that 20 min (cut b) after injection of staphylococcal toxin in a dose of 0.75 ml/kg, bradycardia, slowing of respiration, and synchronization of the EEG were observed. One hour after injection (cut c), in the control dog a change took place to the tachycardiac phase, accompanied by flattening and desynchronization of the EEG. Cuts d and e reflect the continuation of the tachycardiac phase which changed after $4\frac{1}{2}$ h to a collapse state, with the appearance of Aschoff-Taware rhythm without a P wave, accompanied by apnea and disappearance o of the cortical electrical activity. In the dog receiving morphine the anabolic phase continued to be recorded for 4 h (cuts c and d). Besides the bradycardia and bradypnea, the EEG continued to show slow, high-amplitude potentials of the theta-and delta-rhythm type. Not until $4\frac{1}{2}$ h had elapsed (cut e) was a change observed to the tachycardiac phase, with an increase in the respiration rate and desynchronization of the EEG. This phase continued for 20 h.

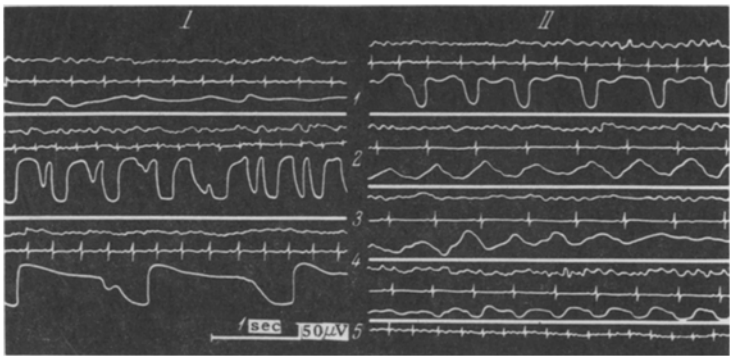

Fig. 3. EEG, ECG, and respiration in a puppy 7 days old. I) control puppy (without injection of morphine); II) experimental puppy (preliminary injection of morphine in a dose of 10 mg/kg): 1) before injection of staphylococcal toxin in a dose of 1 ml/kg; 2) 1 h after injection; 3) 3 h; 4) 4 h; 5) 24 h after injection.

An important characteristic of the anabolic phase was that, in addition to the other indices, the EEG showed synchronization. It has been shown in our laboratory that the slow potentials appearing after administration of sedative doses of barbiturates are accompanied by a fall in the concentrations of inorganic phosphorus and lactic acid and by the accumulation of glycogen in the cerebral cortex of animals [9]. In face of these findings, the prolonged maintenance of the slow, high-amplitude potentials during the bradycardic phase in the dogs receiving morphine and staphylococcal toxin may be regarded as an expression of the anabolic trend of metabolism in the cerebral cortex. Together with the increase in the potential lability of the heart [19], this evidently plays an important role in the increased resistance and tolerance of the animals. The electroencephalographic findings during the bradycardic phase of staphylococcal poisoning give a more detailed insight into the results obtained by several of the authors cited above, who observed an alleviating effect of certain anesthetics on the course of bacterial poisoning.

Let us now consider the effect of morphine on the course of staphylococcal poisoning in the puppies of the 1st group. Investigations in our laboratory [1,3,4,10,11,17-21] have shown that because of the absence of tone in the center of vagus regulation of cardiac activity the reactions of very young puppies (under 18-20 days old) to bacterial toxins are determined by changes in the tone of the sympathetic innervation. No anabolic phase is present. Tachycardia always appears at first, and is followed by protracted collapse.

However, tonic excitation of the center of vagal innervation may also arise episodically even in very young puppies in hypoxic states and during an increase in intracranial pressure [5,20]. We have previously shown [19] that bradycardia of vagal origin with respiratory arrhythmia, which can be abolished with atropine, develop gradually in puppies lying freely on a heated surface at a moderate temperature and unanesthetized, following the subcutaneous injection of morphine in a dose of 10-20 mg/kg (Fig. 2).

In this connection the question arose whether in very young puppies it was not possible to produce the appearance of the anabolic phase during staphylococcal poisoning by the preliminary administration of morphine. A series of experiments was carried out on 16 puppies of the 1st age group. Control puppies received an injection of staphylococcal toxin alone, while the experimental animals received a subcutaneous injection of morphine in a dose of 10 mg/kg 30-40 min before the injection of the toxin. Staphylococcal toxin was injected subcutaneously in a dose of 1.0-1.5 ml/kg. The subcutaneous route was preferred for injection of toxin into this group of animals because the puppies died quickly after intravenous injection. Subcutaneous injection prolonged the survival period and enabled the efficacy of therapeutic procedures to be compared. After the subcutaneous injection of staphylococcal

toxin in a dose of 1.0-1.5 ml/kg, no anabolic phase appeared in the very young control puppies. The primary reaction was invariably a tachycardiac phase, and this passed into a stage of collapse. The duration of survival was 24-48 h. In each experiment puppies of the same age and weight, in the same condition, and from the same litter were chosen. Usually two puppies (one control and one experimental) took part in the experiment.

In the very young experimental puppies, receiving a preliminary injection of morphine, a very well defined initial bradycardic phase was recorded during staphylococcal poisoning, lasting for between 1.5 and 4 h, whereas the purely morphine bradycardia with the same dose lasted for only 30-40 min.

It is clear from Fig. 3 that in the control puppy the initial reaction was tachycardia, giving way after 3 h to the development of protracted collapse with a progressive slowing of the heart rate. In the experimental puppy, injection of toxin against the background of morphine bradycardia intensified the latter still further. The heart rate was slowed from 170 to 100 beats/min. In some experiments a still more marked decrease in the heart rate was observed—to 80-70/min. The tachycardiac phase did not appear until the 4th hour of poisoning and continued for 24 h or longer. In the course of the bradycardic phase the amplitude of respiration fell slightly. The frequency characteristics of the cortical electrical activity remained unchanged; sometimes the electrical activity assumed the character of "bursts." The amplitude of the potentials fell slightly. With the development of the tachycardiac phase a small increase in the amplitude and frequency of the potentials and an increase in the respiration rate were observed.

Hence, the preliminary injection of morphine causes marked changes in the course of staphylococcal poisoning in very young puppies: not only does an initial bradycardic, anabolic phase appear, but the tolerance of the animals to staphylococcal toxin also is increased. The duration of survival of puppies receiving preliminary morphine was significantly longer than that of the control animals, varying from 2 to 10 days.

The experiments showed that the administration of morphine as a cholinergic factor not only prolongs the anabolic phase in staphylococcal poisoning in adult animals, but also causes its appearance in very young puppies, in which it usually is not found. Whereas in adult dogs morphine apparently potentiates the cholinomimetic properties of the bacterial toxin, in very young animals it creates the conditions for their manifestation. The reaction of the puppies receiving morphine is the result of summation of the parasympatheticomimetic effect of morphine with the cholinomimetic action of the staphylococcal toxin.

In conclusion, it must be pointed out that, unlike Selye [23] and Laborit and Huguenard [22], who assessed the initial phase of the reaction to stressor stimuli as an alarm reaction or a shock reaction, we attribute an important adaptive significance to it. In the course of the initial bradycardic phase reserves accumulate (the potential lability is increased) for a reaction of wider range and longer duration in the subsequent catabolic phase or in what Selye calls the stage of resistance.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.