EFFECT OF INTERFERENCE WITH THE NEUROHUMORAL REGULATION OF HOMEOSTASIS ON THE COURSE OF PROTRACTED COLLAPSE IN YOUNG ANIMALS

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Protracted collapse developing in young animals after injection of sublethal doses of chloral hydrate is prevented by preliminary administration of iproniazid (a monoamine oxidase inhibitor) and is irreversibly intensified, terminating in death, after preliminary injection of eserine (an acetylcholinesterase inhibitor).

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Investigations conducted in Arshavskii's laboratory have shown that young animals, unlike adults, cannot respond by adaptive reactions which would enable them to maintain homeostasis during changes in environmental conditions. During the action of various pathogenic stimuli (especially pharmacological agents in large doses), the young animal responds by a gradual transition to a lowered level of activity which continues for a varying length of time. This state, reversible or irreversible depending on the intensity of the stimulus applied, has been called protracted collapse [1, 2, 4, 6-9, 11].

The early age period is characterized by predominance of sympathico-adrenal mechanisms of regulation of homeostasis [1-3, 7, 10, 12], but during the development of protracted collapse adrenergic mechanisms are virtually replaced by cholinergic [2, 5, 6, 8].

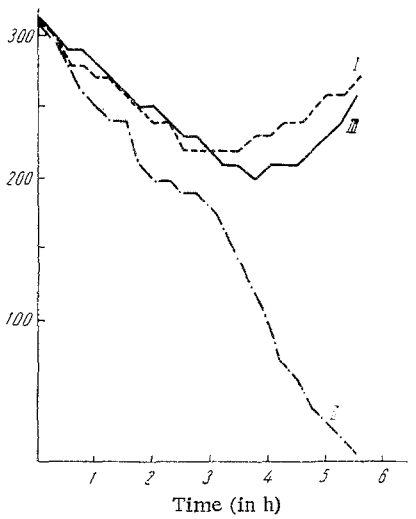

Fig. 1. Changes in cardiac activity following intraperitoneal injection of chloral hydrate into rabbits aged 5 days. I) Iproniazid; II) eserine; III) control.

The transition into a state of protracted collapse was studied in the present investigation during interference with adrenergic and cholinergic mechanisms of neurohumoral regulation.*

EXPERIMENTAL METHOD

The experiments of series I were carried out on 18 rabbits aged 4-6 days, and those of series II on 14 puppies aged 9-10 days. Three animals from the same litter were used in each experiment. One animal first received iproniazid (a monoamine oxidase inhibitor, facilitating accumulation of catecholamines); the second received eserine, blocking cholinesterase, at the same time; the third acted as control. To produced a state of collapse chloral hydrate was injected intraperitoneally in a sublethal dose of 400 mg/kg. Iproniazid and eserine, in a dose of 1 mg/kg, were injected subcutaneously 45-60 min before the chloral hydrate. The ECG was recorded throughout the experiment. The body temperature, changes in which were recorded by means of an ETM-3B electrothermometer, was used as an additional criterion of the transition into the state of collapse.

* A. V. Piskarev, a student at Tomsk University, helped with the investigation.

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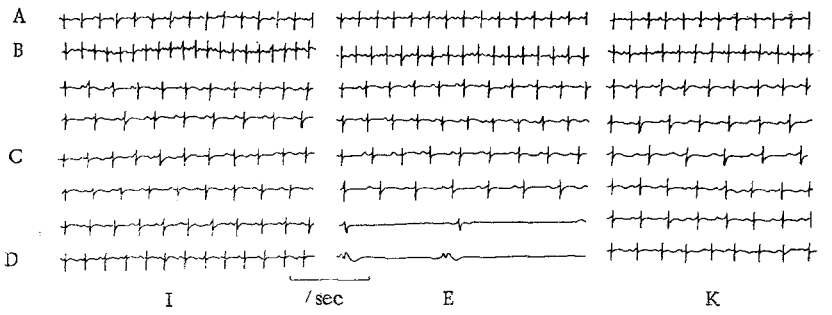

Fig. 2. Changes in cardiac activity following intraperitoneal injection of chloral hydrate into puppies aged 10 days. I) Iproniazid; E) eserine; K) control; A) initial rate; B) rate after injection of chloral hydrate; C) development of reversible collapse in K (control) and its absence in I (after preliminary injection of iproniazid); D) heart rate 4 h after injection of chloral hydrate.

EXPERIMENTAL RESULTS

The control rabbits responded initially to injection of chloral hydrate by an increase in the degree of tonic excitation of the sympathetic centers of the heart, manifested by some increase in the heart rate or by maintenance of its original level. The duration of the first phase, when a state of homeostasis was maintained, was up to 1 h. The first phase was followed by the second, transition into a state of protracted collapse. This reached its maximal intensity 2.5-4 h after injection of chloral hydrate and was characterized by a gradual fall in the body temperature and slowing of the heart rate, due to a decrease in the degree of tonic excitation of sympathetic centers of cardiac regulation. These results were in agreement with those previously obtained in Arshavskii's laboratory [5, 6, 8].

With the sublethal dose of chloral hydrate used, the state of collapse was reversible in every case and after a short time the cardiac activity and the body temperature returned to their original level. Both these functions were restored to normal after about 24 h. The change in the character of the response caused by interference with the adrenergic and cholinergic mechanisms of neurohumoral regulation, compared with the response of the control rabbits, is illustrated in Fig. 1. After injection of iproniazid the duration and course of the first phase of the response differed only slightly from those in the control. The second phase was characterized by a more gradual decrease in the heart rate than in the control animals. The course of collapse was shorter in duration and the transition to the initial state took place more rapidly than in the controls.

Preliminary injection of eserine, on the other hand, shortened the duration of the first phase of the response and led to a more rapid transition to a state of collapse and a more decrease in heart rate and body temperature. The rapidly progressive collapse under these circumstances was irreversible in all cases and ended with death of the animals 4-5 h after injection of the sublethal dose of chloral hydrate.

According to Bozkovy and co-workers [13], young animals in the early period of development possess low monoamine oxidase activity, which increases by the 14th day of life. It was therefore interesting to investigate the effectiveness of iproniazid in puppies aged 10 days in which higher monoamine oxidase activity than was present in the young rabbits could be assumed to exist. After preliminary injection of iproniazid into these puppies, the first phase of the response to injection of chloral hydrate was manifested particularly clearly. Whereas in the control animals this phase took the form of a prolonged maintenance (for 1 h) of the original heart rate, in the animals preliminarily receiving iproniazid it was characterized by an increase in the heart rate by 30-60 beats per minute (Fig. 2). The entire response to the anesthetic in fact consisted of the first phase only.

The increase in heart rate after injection of chloral hydrate into animals previously receiving iproniazid can be explained by an increase in the ability of the body to maintain an increased concentration of catecholamines for a longer period in response to the action of a stressor. Under these circumstances the concentration of catecholamines is evidently increased because of their slower breakdown. Preliminary injection of eserine resulted not only in a more rapid transition into the state of collapse, but also in lethal outcome.

The results confirm the view that transition into a state of collapse in young animals is due to exhaustion of the sympathico-adrenal factors of regulation. Iproniazid, a monoamine oxidase inhibitor, increases, while eserine, a cholinesterase inhibitor, decreases the resistance of the young animal and its tolerance to the toxic action of chloral hydrate.

These results, like those of previous investigations [1, 7], indicate that in the search for measures of management of protracted collapse at an early age, preference must be given to procedures which facilitate maintenance of the sympathico-adrenal mechanisms of regulation of homeostasis at a high level.

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