RESTORATION OF DISTURBED RESPIRATION IN CATS BY THYROTROPHIN RELEASING HORMONE

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In the study of problems in modern physiology and biochemistry of neuropeptides an important place is occupied by research aimed at explaining their role in the regulation of concrete autonomic functions and, in particular, of respiration. Thyrotrophin releasing hormone (TRH) is particularly interesting from this aspect. There are data in the literature [1, 4, 6, 8] on its stimulating effect on respiration. TRH is found in the brain stem and, specifically, in that part of the medulla where the respirator center is located in warm-blooded animals [9]. Elucidation of the role of this substance when activity of the respiratory center is disturbed is particularly interesting. However, there are only sporadic data on this matter, which indicate that TRH helps to restore respiration during anoxia induced by acute blood loss [2].

It was decided to study wheter, with the aid of TRH, respiration disturbed as a result of certain experimental procedures can be partially or totally restored. Investigations of this kind are important from not only the theoretical but also the practical point of view, for in many operations, especially on the thoracic organs, artificial stimulation of the respiratory center may be necessary. The results of such an investigation are described in this paper.

EXPERIMENTAL METHOD

Experiments were carried out on 20 cats anesthetized with pentobarbital (40 and 50-60 mg/kg body weight). Respiratory movements were recorded by means of a carbon transducer. The electromyogram (EMG) of the diaphragm was recorded by means of wire electrodes, with bent tips. The EMG of the diaphragm served as an indicator of the state of the respiratory center. The UBP-2-03 biopotentials amplifier was used. TRH (Pyroglutamyl-histidyl-prolinamide), in a dose of 20-30 μg/kg, was injected into the femoral vein (2 ml of solution). In control experiments the same volume of physiological saline was injected. To connect the artificial respiration apparatus ("Vita-1") tracheotomy was performed. In one series, bilateral vagotomy was performed.

EXPERIMENTAL RESULTS

Investigation of the action of TRH on respiration of anesthetized cats in six of seven experiments showed that the substance, in a dose of 20-30 μg/kg, caused quickening of respiration after 15-30 min (on average by 10-20%). Normalization of respiration in cases when it was unstable, or when the pattern of inspiration or expiration differed from normal, was characteristic of these experiments. In the course of the experiments it was also discovered that in some cases the animal came round from the anesthetic under the influence of TRH, and for that reason in all subsequent series the dose of pentobarbital was increased to 50-60 mg/kg.

The experiments were set up in two modifications. In the first modification (five experiments) artificial hyperventilation was used until activity of the diaphragm ceased, evi-

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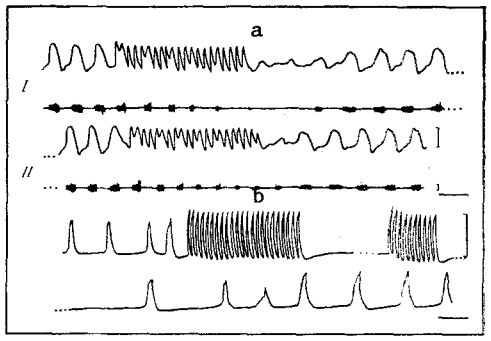

Fig. 1

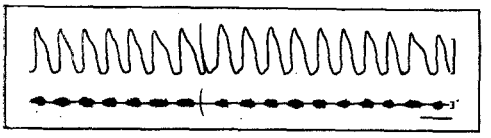

Fig. 2

Fig. 1. Action of TRH on effects of hyperventilation. a) Prevention of inhibition of respiratory activity by means of TRH: I) pneumogram and EMG of diaphragm before injection of TRH, II) after injection of TRH; b) restoration of breathing (pneumogram) after its arrest caused by hyperventilation, by TRH. Here and in Figs. 2 and 3, dotted lines indicate interruptions in recording. Calibration: 25 ml, 100 μV, 10 sec.

Fig. 2. Absence of changes in respiratory activity after vagotomy preceded by injection of TRH.

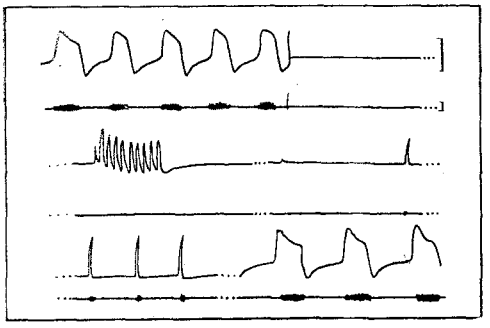

Fig. 3. Restoration of respiration after its arrest by vagotomy.

dence of arrest of spontaneous activity of the respiratory center. In seven experiments hyperventilation was used after preliminary injection (15-20 min beforehand) of TRH (in a dose of 20-30 μg/kg); under those circumstances arrest of spontaneous respiration as a rule was not observed. Under these conditions, throughout the period of artificial ventilation, activity of the diaphragm was preserved and the period of the after-effect, namely the slowing of respiration which usually arises after cessation of artificial respiration, was shortened (Fig. 1a).

In one experiment, the animal's breathing was initially very slow. Against this background, hyperventilation led to cessation of spontaneous respiration, which continued for a long time — 15 min after disconnection of the apparatus for artificial ventilation. In this period, to keep the animal alive, the apparatus was periodically switched on. TRH was injected immediately after respiratory arrest in a dose of 20 μg/kg, but respiration began to recover only after an additional injection of 30 μg/kg, of the compound. Gradually over 25-30 min the respiration rate returned to normal (Fig. 1b). In the second modification (eight experiments) bilateral vagotomy was performed, causing slowing of respiration by 30-40%. TRH in a dose of 20-30 μg/kg in all experiments either abolished this effect completely, if the substance was injected 10-20 min before vagotomy (Fig. 2), or reduced it on the average by 30% (three experiments). In this series also, in one experiment vagotomy led to prolonged (20 min) respiratory arrest, which was restored after two injections of TRH in a dose of 20 μg/kg; under these circumstances it assumed the form characteristic of cats with bilateral vagotomy (Fig. 3). TRH also had a similar action on respiratory arrest induced by hyperventilation preceded by bilateral vagotomy. In both modifications of the experiments control injection of physiological saline had no action on the effects of hyperventilation or vagotomy.

TRH thus had the property of restoring respiration partially or completely, when disturbed as a result of certain experimental procedures. The results are evidence of the regulatory action of TRH on breathing. Our experiments showed that TRH can normalize a disturbed pattern of respiration and can quicken the respiration of anesthetized cats. The data agree with results obtained by other workers, who showed that TRH induces tachypnea in rats [4, 5], cats [6], rabbits [7], and monkeys [8]. Preservation of the effect described above even after brain transections above the pons [7] is very important. This fact is indirect evidence that the activating effect of TRH on respiration is evidently realized through its effect on bulbar structures of the respiratory center, without the participation of higher levels of the brain and, in particular, of the hypothalamus. These views are supported by information in the literature [3] showing that TRH has a stimulating action directly on neurons of the respiratory center. Our own data indicate that TRH restore activity of the respiratory center after total cessation of its spontaneous activity. As regards the mechanism of this action of TRH, it can only be postulated that neurons of the respiratory center may perhaps possess the lowest threshold for the action of TRH as a neuropeptide which, as we know, has a stimulating action on any structures of the CNS. This hypothesis was confirmed in the present investigation by the fact that the anesthetized animals awoke under the influence of TRH.

To sum up the results briefly, it can be concluded that TRH can help to restore spontaneous activity of the respiratory center of anesthetized cats, when "silent" as a result of an artificial experimental procedure.

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