THE EFFECT OF ANALGESICS ON REFLEXES FROM THE PERICARDIUM AND THE HILAR REGION OF THE LUNGS DURING HYPOTHERMIA

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The use of analgesic drugs affecting the interoceptive reflexes in thoracic surgery has created interest in the study of the effect of these drugs during hypothermia. In the present work we investigated the action of morphine, promedol and phenadone on the reflex changes in the blood pressure in response to stimulation of the pericardium and the hilar region of the lung during hypothermia (30-32° and 25-27°).

EXPERIMENTAL METHOD

Experimental were carried out on 52 cats weighing from 2.5 to 4 kg. In order to produce hypothermia, the animals were anesthetized with urethane (1.2-1.4 g/kg) and placed in a double-walled metal bath, through which cold water was passed so as to maintain the body temperature of the animal at a constant level throughout the experiment.

Increase in the Depressor Vascular Reactions in Response to Stimulation of the Pericardium and Hilar Region of the Lungs under the Influence of Analgesics (as % of the Normal Value) at Different Body Temperatures (Mean Values)

Drug	Dose (in mg/kg)	36–38°		30–32°		25–27°	
		peri-cardium	hilum of the lungs	peri-cardium	hilum of the lungs	peri-cardium	hilum of the lungs
Morphine	2,0	150	183	155	124	138	139
	5,0	140	196	131	158	120	144
Promedol	1,0	126	138	114	134	100	100
	3,5	117	120	112	108	105	100
Phenadone	1,0	123	116	125	115	119	103

*Note. The value of the depressor reflex before injection of the analgesic (normal) is taken as 100%.

The pericardium was stimulated by inflating it with air through a special cannula. The degree of distension, which was measured by a water manometer, was constant in all the experiments (60-80 mm of water).

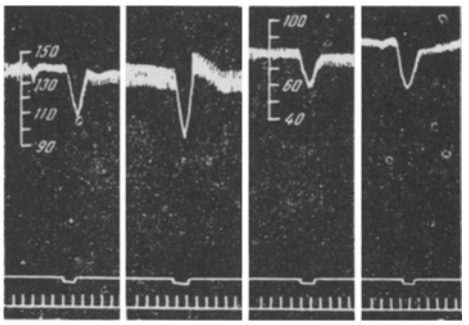

Fig. 1. Effect of morphine (2 mg/kg) on the reflex changes in the blood pressure in response to stimulation of the pericardium at a normal temperature (left half of kymogram) and during hypothermia to 25-27° (right half of kymogram). a) before injection of the drug; b) 60 minutes after injection. Significance of the curves (from above down): blood pressure, stimulus marker, time marker (5 seconds).

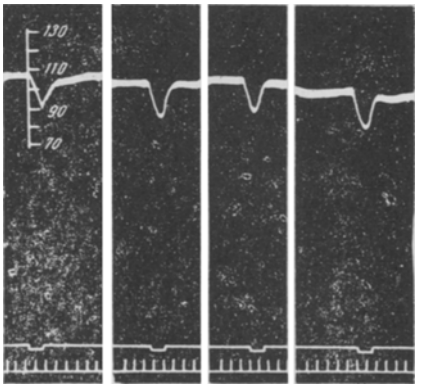

Fig. 2. Effect of promedol (1 mg/kg) on the reflex changes in the blood pressure in response to stimulation of the hilar region of the lungs during hypothermia to 25-27° a) before injection of promedol; b) 10 minutes after injection; c) 30 minutes after; d) $1^1/_2$ hours after. Significance of the curves as in Fig. 1.

cooled to 30-32° (see table).

The hilar region of the right lung was stimulated by being stretched with a weight of 115 g through a system of pulleys. The blood pressure was recorded in the usual manner. The analgesics were injected intravenously in the following doses: morphine 2 and 5 mg/kg, promedol 1 and 3.5 mg/kg and phenadone 1 mg/kg.

So that the results obtained should be comparable, we first investigated the effect of hypothermia on the reflex lowering of the blood pressure in response to stimulation of the receptive zones of the pleural cavity, and the effect of analgesics on this reaction at a normal temperature—36-38°. The action of the analgesics was then studied during hypothermia (30-32° and 25-27°). In order to compare the results obtained, the value of the depressor reaction before and after injection of the analgesic was calculated as a percentage of the initial (at the moment of stimulation) level of the blood pressure. The ratio between the value of the vascular reaction (in %) after injection of the analgesic and the value of the vascular reaction (in %) before injection of the drug was used as an index of its effect on the depressor reflex.

EXPERIMENTAL RESULTS

In all the experiments on animals at normal temperature and during hypothermia to 30-32°, the magnitude and character of the reflex response to stimulation of the receptor zones were almost identical. During hypothermia to 25-27° a fall in the reflex responses to two-thirds their previous magnitude was observed. An increase in the intensity of stimulation led to an increase in the depressor reaction. Restoration of the initial level of the reflexes usually took place after warming to 34-35°.

The effect of the analgesics investigated on the reflex reactions in response to mechanical stimulation of the pericardium and of the hilar region of the lungs followed the same pattern, and was expressed as an increase in the depressor reflex.

Injection of morphine in doses of 2 and 5 mg/kg, at 36-38°, caused an increase in the depressor reaction after 10-15 minutes to 125-136% in response to stimulation of the pericardium, and to 160-194% in response to stimulation of the hilar region of the lungs (the magnitude of the depressor reaction before injection of the analgesic was taken as 100%). Maximum increase in the depressor reaction was observed 50-60 minutes after injection of morphine (see table) and it continued for $1^1/_2$-2 hours (dose 2 mg/kg) or much longer (dose 5 mg/kg). A similar effect was shown by morphine in response to stimulation of the paricardium in animals

During hypothermia to 25-27° the action of morphine in enhancing the vascular reflexes was appreciably weakened. This is illustrated by Fig. 1, in which it is shown that the action of morphine in a dose of 2 mg/kg at a normal temperature was more pronounced than during hypothermia to 25-27°.

Hypothermia to 30-32° and 25-27° appreciably lowered the effect of morphine (2 and 5 mg/kg) on the reflexes from the hilar region of the lungs. Whereas, for instance, in a dose of 5 mg/kg and at a normal body temperature, morphine almost doubled the magnitude of the depressor reaction, during hypothermia its action was less pronounced (see table).

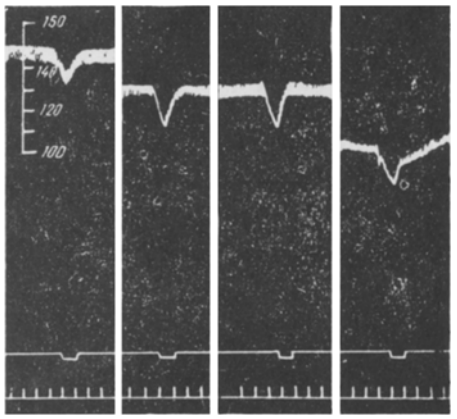

Fig. 3. Effect of phenadone (1 mg/kg) on the reflex changes in the blood pressure in response to stimulation of the hilar region of the lungs during hypothermia to 30-32°. a) before injection of the drug; b) 10 minutes after injection; c) 60 minutes after; d) 2 hours after. Significance of the curves as in Fig. 1.

The effect of promedol on the reflex changes in the blood pressure in experiments on animals at the normal temperature and in hypothermia differed from that of morphine under the same conditions. In the first place, the action of promedol in doses of 1 and 3.5 mg/kg in enhancing the depressor vascular reflexes was almost identical whatever the range of temperatures. Secondly, in the doses which we studied, promedol had a weaker effect on the reflex changes in the blood pressure than did morphine at the same temperatures. Thirdly, in contrast to morphine, the action of promedol was diminished in parallel with the fall in body temperature, and in hypothermia at 25-27°, generally speaking, it was absent (Fig. 2).

The effect of phenadone (1 mg/kg) on the vascular reflexes in response to stimulation of the two receptor zones at the normal body temperature and in hypothermia differed from the action of the two previous analgesics. At all body temperatures studied, phenadone had an equally feeble effect on the depressor reactions (see table and Fig. 3). Its action was brief duration, and usually passed off from 1-1$^1/_2$ hours after administration.

It must be pointed out that our experiments at different temperatures failed to show any relationship between the degree of enhancement of the depressor reaction and the dose of analgesic. On the contrary, in large doses, morphine and promedol had a less marked enhancing action on the vascular reflexes than in doses of 1-2 mg/kg. In the experiments with phenadone a similar picture was seen. This was shown by the results of additional experiments during hypothermia to 32-33°, in which no sharp increase in the enhancing effect was observed when phenadone was given in repeated small doses up to a total dose of 6 mg/kg.

Our investigations showed that during hypothermia the enhancing action of analgesics on the interoceptive vascular reflexes is lessened. This effect may be associated with alteration of the functional state of the reflex centers at a low body temperature, due primarily to changes in the functional state of the synapses, which are very sensitive to cooling.

According to Glick [5], Nachmanson et al. [8] and others, during hypothermia changes take place in the cholinesterase and cholinacetylase activity, i.e. the chemical component of synaptic transmission is disturbed. There is no doubt that a change in the reactivity of these enzyme systems is a manifestation of the universal depressing effect of cold on the action of all enzymes, for these are other indications in the literature of the diminished intensity of various enzymic reactions during a fall in the body temperature [3, 6, 7].

The investigations of V. V. Zakusov and his co-workers proved convincingly that the point of application of the action of analgesics is the synapses in the central nervous system (diencephalon [2], spinal cord [1, 4]). Changes in the effects of analgesics on the interoceptive reflexes from the thoracic organs during hypothermia should be regarded as the result of an alteration in the functional state of the central links of the reflex arc, in consequence of the fall in the body temperature.

SUMMARY

The author studied the effect of morphine (2 and 5 mg/kg), promedol (1 and 3,5 mg/kg) and phenadone (1 mg/kg) on the reflex changes of the blood pressure after stimulating the pericardium and the area of the hilum of the lung at normal temperature and in hypothermia (30-32 °C and 25-27 °C).

Experiments were performed on cats. Analgesics intensify the depressor vascular reflexes at normal temperatures; at lower temperatures this action is less pronounced. The change in the analgesic effect on the interoceptive reflexes from the thoracic organs in hypothermia should be regarded as the result of the altered functional condition of the central links in the reflex arc due to lowered body temperatures.

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