THE EFFECTS OF GENERAL ANESTHETICS, ANALGESICS, AND CHLORPROMAZINE ON REFLEX REACTIONS ORIGINATING IN THE VESSELS OF THE PULMONARY CIRCULATION

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It is well known that if veratrine [14], serum [15], or other substances are injected into the circulation, complex reflex reactions arise, in the form of hypotension, bradycardia, and changes in the rate and depth of respiration. It has been shown that these reactions are the result of afferent impulses from various vascular receptor zones: the coronary vessels [16, 17, 18, 24], the carotid sinus zone [21], and, especially, the pulmonary vessels. The last of these has been demonstrated by an original method involving the injection of stimulating substances (veratrine, aconitine, nicotine, and ammonium chloride) into a lobe of the lung that has been isolated from the circulation [5], and of veratridine, by catheterization of the right side of the heart or the pulmonary artery [13].

The latent period for reflexes originating in the receptors of the pulmonary vessels is 3-4 seconds, when the stimulating substance is injected into the right atrium [19]. The reflex reactions that appear after 8-10 seconds or more can be attributed to the influence of the chemical substances on the receptors of the coronary vessels, as well as their direct effect on the central nervous system [23].

Since afferent impulses from the receptors of the pulmonary vessels reach the brain stem only by way of fibers in the vagus nerve, the central components of these reflexes have synapses in the more caudal portion of the medulla. It is known from the work of V. V. Zakusov [6, 7, 8] that reflexes having synapses at this level in the central nervous system – e.g., the respiratory reflexes – are characterized by their stability to general anesthetics. This is in agreement with the fact that physiological investigations of reflexes from the lungs have usually been carried out on animals under general anesthesia. At the same time, individual general anesthetics show marked differences in their effects on different portions of the reticular formation of the brain stem [3, 4]. There is no doubt that depression of the functions of various brain stem structures by general anesthetics, analgesics, and neuroplegics can affect the character of reflexes from the pulmonary vessels.

The paucity of investigations in this area and the practical interest in the depression of reflexes from the lungs led us to study the effects of urethan, pentobarbital, hexobarbital, morphine, promedol, and chlorpromazine on the complex reflex reactions arising in response to injection of the stimulating agent into the vessels of the pulmonary circulation.

Injection of Stimulating Substances into a Pulmonary Lobe Isolated from the Circulation

Experiments were carried out by the method developed in the Institute of Pharmacology and Chemotherapy, USSR Academy of Medical Sciences, on cats anesthetized with urethan (1.3 mg/kg intraperitoneally). In this series of experiments we studied the effect of morphine and promedol on the hypotension and bradycardia originating reflexly from the receptors of the pulmonary vessels. Each experiment was performed on two cats, one of which served as donor, supplying blood to a lobe of the other cat's right lung, which was isolated from the rest of its circulation. In the second cat, femoral artery blood pressure and pulse were recorded on a kymograph drum by means of a mercury manometer. The donor underwent bilateral vagotomy for the prevention of reflex cardiovascular reactions on the donor side. Following data from special studies in this area [20], bovine serum stored for 8-10 weeks was used as a stimulating agent, and when 3-4 ml of this was injected into the artery of the isolated pulmonary lobe, typical reflex reactions resulted. Artificial respiration was used for both cats. Because of the desensitization of vascular receptors to serum [18], as well as to other substances [5], morphine and promedol were injected into the femoral vein in doses of 1 mg/kg ten minutes before serum was injected into the isolated lobe.

Hypotension and bradycardia were observed both after promedol and after morphine. In three experiments analgesics were injected during the period between the first and second serum injections. In this group of experiments morphine failed to reduce the hypotensive reaction, and the bradycardia was even more pronounced (Fig. 1). The change in the magnitude of reflex reactions under the influence of promedol was difficult to evaluate, since the observed diminution might result from desensitization of the receptors to the stimulus.

Thus, from these experiments we could conclude that both morphine and promedol are ineffective in preventing these reflex cardiovascular reactions from the receptors in the pulmonary vessels. The change in the magnitude of these reflex reactions under the influence of analgesics was investigated in the next series of experiments.

Injection of Stimulating Substances into the Right Atrium

Investigations were carried out on cats anesthetized with urethan injected intraperitoneally and supplementally by vein, and also on rabbits without anesthesia. Stimulating substances were injected into the right atrium by a catheter; in experiments on cats the substance used was serum, and in experiments on rabbits it was veratrine hydrochloride (15-20 μg in 0.005% solution), since serum evoked a barely perceptible reaction in rabbits. Respiration was recorded, and blood pressure and pulse were recorded from the common carotid artery. In estimating the magnitude of the hypotensive reaction in these experiments, we considered only the "primary" hypotension determined 5-6 seconds after injection of the stimulating substance into the right atrium and reflecting reflexes exclusively from the pulmonary vessels [19]. In view of the fact that a number of authors [5, 18, etc.], have reported desensitization of receptors of the pulmonary vessels upon frequent injection of stimulating substances, these substances were injected at intervals of 20-25 minutes. Under these conditions the reflex reactions retained their intensity through 4-5 repeated injections of serum into cats and veratrine into rabbits, in control experiments. All the pharmacological substances were injected intravenously by the drop method.

In this series of experiments morphine and promedol in doses of 1 mg/kg showed an inconstant effect on the cardiovascular component of the reflex reaction in cats. Thus, out of eight experiments with promedol, hypotension and bradycardia increased (by 10-20%) in three (Fig. 2a), were briefly diminished (by not more than 30%) in four, and remained unchanged in one. Of five experiments with morphine, an increase (20%) in the hypotension and bradycardia was noted in three experiments, and no change was observed in two.

In the experiments on rabbits, injection of promedol in a dose of 1 mg/kg generally caused an initial reduction (40-50%) in cardiovascular reactions, with subsequent elevation to the original level. Morphine (in a dose of 1 mg/kg) had essentially no effect on the hypotension and bradycardia, or slightly enhanced them.

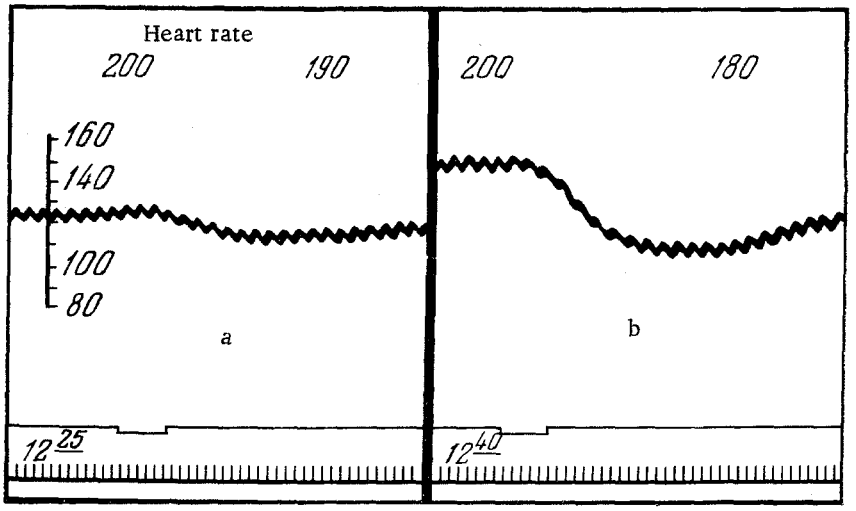

Fig. 1. Reflex reactions upon injection of serum (4 ml) into lobe of right lung isolated from circulation, before (a) and 13 minutes after (b) injection of morphine (1 mg/kg). Cat weighing 3.2 kg; anesthesia–urethan, 1.3 mg/kg intraperitoneally. Figures are heart rate calculated as beats per minute. Interpretation of curves (top to bottom): blood pressure, marker indicating serum injection, time marker (1 second).

As regards the respiratory component of this reaction– under the influence of analgesics, especially promedol, the appearance of an expiratory respiratory pause or the lengthening of this pause was observed. This pause was more pronounced in cats, particularly in those experiments where intensification of bradycardia was observed (see Fig. 2a). In rabbits this effect was observed later than in cats, and also coincided with the moment of intensification of bradycardia.

In the experiments on cats urethan in a dose of 1-1.25 mg/kg had no noticeable effect on the cardiovascular reactions. The character of the respiratory reflex was determined from the depth of anesthesia: in incomplete anesthesia an increase in the amplitude of respiration was observed, and when anesthesia was deepened by injection of urethan into the vein, a respiratory pause appeared in the expiratory phase (Fig. 2b). In rabbits hexobarbital in a dose of 35 mg/kg (2/3 of the anesthetic dose) completely reversed the bradycardia and reduced hypotension (by 40-50%). Pentobarbital in doses of 5 mg/kg in rabbits (1/5 of the anesthetic dose) and 10-15 mg/kg in cats (1/3-1/2 of the anesthetic dose) greatly weakened the whole reflex complex: the hypotension was depressed by 70-80%, and the bradycardia completely, the respiratory reaction also being reduced (Fig. 3).

In experiments on cats, chlorpromazine in a dose of 1-2 mg/kg reduced all three components of the re-

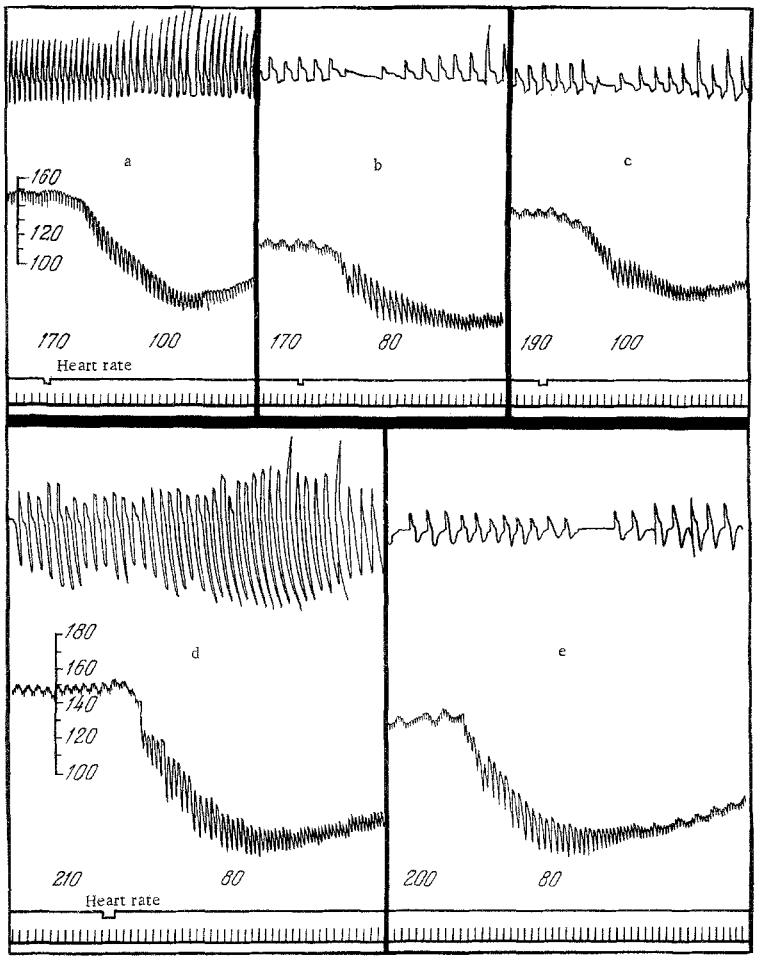

Fig. 2. I. Reflex reactions to injection of serum (0.8 ml) into the right atrium, before (a), ten minutes after (b), and 30 minutes after (c), injection of promedol (1 mg/kg). Cat (weight 4.8 kg); incomplete anesthesia – 1 mg/kg intraperitoneally. II. Reflex reactions to injection of serum (0.8 ml) into the right atrium in incomplete urethan anesthesia (d) and after anesthesia was deepened to become complete (e). Cat (weight 3.3 kg); anesthesia – urethan, 1 mg/kg intraperitoneally plus 0.3 mg/kg intravenously. Figures are heart rate calculated as beats per minute. Interpretation of curves (top to bottom): respiration (inspiration is downward), blood pressure, marker indicating stimulus injection into the right atrium, time marker (1 second). Designations as in Fig. 1.

flex reaction by roughly 50%. In this case bradycardia returned to its initial level after 1-1½ hours, whereas the hypotensive reaction remained at the reduced level. In experiments on rabbits, chlorpromazine in a dose of 1-1.6 mg/kg completely suppressed the whole reflex complex, and restoration of these reactions began two hours after it was injected. Since chlorpromazine lowered blood pressure by 40-50%, we carried out control experiments on cats and rabbits, in which the blood pressure was lowered to the same extent by hemorrhage (20-25 ml of blood). The intensity of the hypotension was maintained to the same extent, or was reduced by not more than 10%, and the bradycardia was actually intensified.

It follows from the data above that reflex reactions originating in the receptors of the pulmonary vessels, with afferent impulses proceeding along the vagi, are affected to different degrees by different anesthetics. Urethan, as general anesthesia deepens, "facilitates" expiration without having any material effect on the hypotension and bradycardia. The change in the character of the respiratory reflex indicates that under the influence of this anesthetic the expiratory "center" in the cranial portion of the dorsolateral formation of the medulla is liberated from inhibitory influences exerted by higher divisions of the central nervous system. Thus, the depressant effect of urethan in the brain stem is slight, and in the usual anesthetic doses it does not reach the caudal portion. Pentobarbital in doses of 1/5-1/2 the anesthetic dose markedly inhibits the whole reflex complex; this shows that pentobarbital simultaneously depresses different brain stem structures at the same time, including those that are located in the caudal portion of the brain stem. With hexobarbital this effect is weaker than with pentobarbital. The diminution of bradycardia under the influence of barbiturates is explained, in addition, by their ganglion-blocking action [11, 12].

Morphine and promedol also have different effects on reflexes from the receptors of the pulmonary vessels, a species difference being noted in the action of the latter: in rabbits promedol first inhibits the entire reflex complex to some extent, and then "facilitates" expiration and enhances bradycardia; in cats, on the other hand, the first phase of the action of promedol is almost absent. In both rabbits and cats morphine either has no noticeable effect or else enhances hypotension and bradycardia and "facilitates" expiration. A difference in the action of these two analgesics has also been observed in relation to other effects. For example, promedol is more active than morphine in depressing reflexes originating upon stimulation of the deep portions of the respiratory tract [9], and in depressing inhibition of the knee-jerk reflex elicited by electrical stimulation of the cerebellum [1]. Apparently the depressant effect of promedol in the central nervous system is less selective than is the case with morphine.

Chlorpromazine inhibits the whole reflex complex originating in the pulmonary vessels to a greater or lesser extent, depending on the species of the animal, which is in agreement with data on chlorpromazine suppression of most of the inhibitory and facilitatory structures in the brain stem [10].

The depressant action of chlorpromazine, promedol, and pentobarbital on reflexes from the pulmonary vessels is more constant and more marked in rabbits than in cats. This species difference probably is connected with the functional predominance of the descending activating systems in cats as compared with these systems in rabbits. This may also explain certain peculiarities in the character of the reflexes. For example, in cats the amplitude of respiration increases as a consequence of the intensification of expiration, but in rabbits, inspiration is intensified; in cats, too, bradycardia and hypotension are usually more pronounced. The same species peculiarities in these reflexes have also been observed following injection of serotonin into the circulation [22].

The "facilitation" of expiration and bradycardia observed under the influence of urethan and analgesics should be regarded as the result of the removal by these substances of inhibitory influences from other portions of the central nervous system [2, 3, 4].

Of the analgesics, promedol exerts a diphasic effect on reflexes from the pulmonary vessels in the rabbits, first inhibiting them, and then enhancing bradycardia and "facilitating" expiration. In cats the first phase in the action of promedol is slight and irregular. Morphine either has no effect on these reflexes or else enhances them.

Chlorpromazine completely suppresses the entire reflex complex in rabbits, and in cats, it depresses the complex by not more than 50%.

SUMMARY

The results of the experiments described in this paper demonstrate that the reflex reactions to injection of a stimulating substance into the pulmonary circulation change differently under the influence of different anesthetics: Urethan "facilitates" expiration without affecting the cardiovascular component; pentobarbital tends to depress the whole reflex complex to various degrees; while hexobarbital primarily depresses the bradycardia. The bradycardia may also be reduced on account of the ganglionic blocking action of the barbiturates. Promedol, an analgesic, has a diphasic effect on the reflexes from the pulmonary vessels: It first decreases them and then intensifies bradycardia and "facilitates" expiration. In cats the first phase of the promedol effect is slight and irregular. Chlorpromazine depresses the entire reflex complex completely in rabbits, but by not more than 50% in cats.

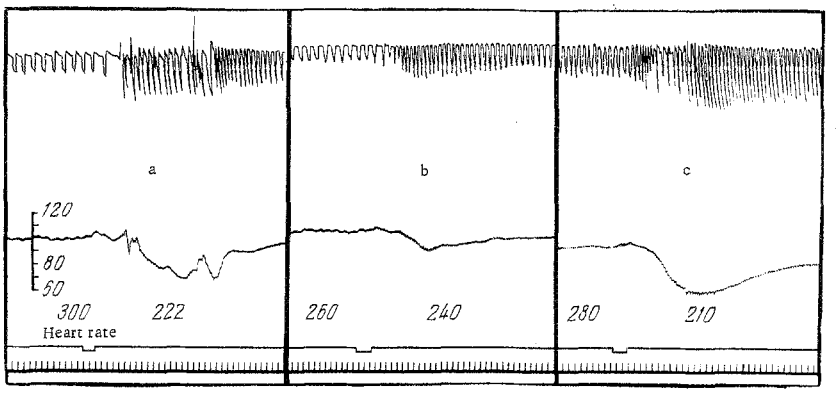

Fig. 3. Reflex reactions upon injection of veratrine hydrochloride (20 μg) into the right atrium, before (a), 5 minutes after (b), and 25 minutes after(c), injection of nembutal (5 mg/kg). Rabbit (weight 2.6 kg); without anesthesia. Designations as in Fig. 2, I.

LITERATURE CITED

1. É. B. Arushanyan, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian] (Leningrad, 1958) p. 87.
2. A. V. Val'dman, Doct. Diss.: The Effect of Analgesics on Inhibitory Processes in the Central Nervous System Accompanying Stimulation of Internal Organs [in Russian] (Leningrad, 1957).
3. A. V. Val'dman, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian] (Leningrad, 1958) p. 64.
4. A. V. Val'dman, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian] (Leningrad, 1958) p. 13.
5. V. V. Zakusov, Farmakol. i Toksikol. 2-3, 35 (1938).
6. V. V. Zakusov, Farmakol. i Toksikol. 5, 31 (1939).
7. V. V. Zakusov, Experimental Data on the Pharmacology of the Central Nervous System [in Russian] (Leningrad, 1947).
8. V. V. Zakusov, Pharmacology of the Nervous System [in Russian] (Leningrad, 1953).
9. Z. N. Ivanova, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian] (Leningrad, 1958) p. 113.
10. V. P. Lebedev, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian] (Leningrad, 1958) p. 87.
11. D. A. Kharkevich, Cand. Diss.: The Effect of Ganglionic Agents and General Anesthetics on the Transmission of Excitation in the Superior Cervical Ganglion during Stimulation of the Preganglionic Trunk at Different Frequencies [in Russian] (Leningrad, 1953).
12. D. A. Kharkevich, Farmakol. i Toksikol. 1, 3 (1956).
13. D. M. Aviado, R. G. Pontius, and C. F. Schmidt, J. Pharmacol. and Exper. Therap. 97, 420 (1949).
14. A. Bezold and B. Hirt, in: Untersuchungen aus dem physiologischen Laboratorium in Würzburg (Leipzig, 1867) No. 1, p. 73.
15. T. G. Brodie, J. Physiol. 26, 48 (1900).
16. G. S. Dawes, J. Pharmacol. and Exper. Therap. 89, 325 (1947).
17. G. S. Dawes and J. H. Comroe, Physiol. Rev. 34, 167 (1954).
18. G. S. Dawes and W. Feldberg, J. Physiol. 108, 362 (1949).
19. G. S. Dawes and J. C. Mott, Brit. J. Pharmacol. 5, 65 (1950).
20. H. P. Gilding and M. E. Nutt, J. Physiol. 102, 446 (1944).
21. C. Heymans and G. R. Vleesehhouwer, Arch. Internat. Pharmacodyn. 84, 409 (1950).
22. J. A. Schneider and F. F. Jonkman, J. Pharmaol. and Exper. Therap. 111, 84 (1954).
23. E. D. Schwiss and G. L. Maison, J. Pharmacol. and Exper. Therap. 105, 87 (1952).
24. A. Jarisch and H. Richter, Arch Exper. Path. u. Pharmacol. 193, 347 (1939).