Mechanisms of immediate respiratory responses to chlorpromazine

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Schopp, Robert T. Mechanisms of immediate respiratory responses to chlorpromazine. Am. J. Physiol. 197(5): 1075-1078. 1959.—Following the intravenous injection of chlorpromazine (5 mg/kg) in dogs anesthetized with Pentothal-chloralose, respiratory inhibition occurs followed by stimulation. A fall in arterial blood pressure accompanies the respiratory responses. The evidence indicates that a reflex is involved with receptors for the inhibitory response and at least the major portion of the stimulation located in the thorax with afferent pathways in the vagus nerves. The inhibition and stimulation persist when the arterial blood pressure is compensated. The inhibition *and most of the stimulation are eliminated by vagotomy. It is suggested that the respiratory responses are primarily due to the activation of chemical-sensitive receptors. A portion of the stimulation may be related to the fall in blood pressure.

After the intravenous administration of chlorpromazine there occurs an immediate inhibition of respiration followed by stimulation. A rapid fall in arterial blood pressure accompanies the inhibition and a slower pressure recovery ensues in the respiratory stimulation phase. It has been suggested that the respiratory stimulation is related to the depressor response (1, 2). This is a reasonable assumption in the light of what is known of the depressor reflex effects upon respiration acting through the sino-aortic pressoreceptor mechanisms. The respiratory inhibition observed (1, 3) cannot, however, be explained on this basis as it accompanies a fall in arterial blood pressure which usually leads to respiratory stimulation. The purpose of this study is to clarify the mechanisms of these respiratory responses observed following the administration of chlorpromazine.

Methods

Anesthesia was induced in dogs by intravenous injection of Pentothal sodium followed by alpha-chloralose (70 mg/kg). In a few cases pentobarbital sodium was used alone. Blood pressure was recorded from the femoral artery with a mercury manometer. A pneumograph-tambour system was employed to determine respiratory activity. The responses were registered on a smoked-paper kymograph. Arterial blood pressure was compensated by inserting into the abdominal aorta a large 'T' cannula connected to a blood reservoir in which a constant head of pressure could be adjusted to any desired level. The vagus nerves were sectioned at a mid-cervical level. The carotid sinus regions were denervated by treating with phenol or by tying off the connecting vessels and cutting open the sinuses. Chlorpromazine (Thorazine, Smith, Kline & French), 5 mg/kg, was injected into the femoral vein except in the procedure where it is otherwise specified.

Results

Figures 2A, 3A, 4A and 5A demonstrate the blood pressure and respiratory responses to chlorpromazine. These responses are present under either Pentothal-chloralose or pentobarbital anesthesia. In 29 of 36 animals the responses were similar to those evident in the above figures. In the remaining seven animals respiratory inhibition was not complete, and in these cases there was merely a decrease in amplitude followed by stimulation. A significant depressor response, however, consistently occurred. From figure 1 it is apparent that the manifestation and magnitude of these events are dependent upon the rate of injection, i.e. upon the concentration of the drug arriving at the receptor site. When the fall in arterial blood pressure was opposed by the use of a compensator during the administration of chlorpromazine both the respiratory inhibition and stimulation persisted (fig. 2). In four of six dogs respiratory inhibition was not complete when the compensator was used, however, the degree of inhibition was similar to that observed without the compensator. Occlusion of the common carotid and vertebral arteries during, and for a time after, the injection of chlorpromazine failed to suppress these respiratory responses (fig. 3) in the three animals subjected to this procedure. Denervation of the sinus regions in five animals was observed to be virtually without effect upon the respiratory responses (fig. 4). In three of these dogs sinus}

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FIG. I. Effect of varying the rate of injection of chlorpromazine on respiration and blood pressure. In this and subsequent figures the recordings from top to bottom are as follows: respiration; arterial blood pressure; base line and signal; and time (2 sec.).

Fig. 2. Role of the chlorpromazine-induced depressor response in respiratory inhibition and stimulation.

FIG. 3. Effect of occluding the common carotid and vertebral arteries on the respiratory responses following chlorpromazine injection.

DISCUSSION

The results indicate that a peripheral mechanism is primarily responsible for eliciting the respiratory responses which occur following the administration of chlorpromazine. This is based upon the observation that the respiratory inhibition is not evident and the respiratory stimulation is much depressed after vagotomy. Also when the circulation to the brain is impaired by occluding the common carotid and vertebral arteries during, and for a time after, the injection of chlorpromazine, the respiratory inhibition and stimulation are still present. It is possible that a small amount of this agent could still reach the brain via spinal arteries; but, if this does occur it is without effect upon the respiratory responses to chlorpromazine, which are the same with and without occlusion.

The above evidence indicates that the receptors for these respiratory responses are located either in the thorax or abdomen. The latter has been excluded by showing that when chlorpromazine was injected into the aorta at the level of the diaphragm the inhibition was no longer present and the stimulation was less pronounced. The receptors are evidently located more distantly from this injection site, and the agent is less concentrated when arriving at the receptors than when
Fig. 4. Effect of vagotomy followed by vagotomy on the respiratory responses to chlorpromazine.

Fig. 5. Effect of vagotomy on the respiratory responses to chlorpromazine.

Fig. 6. Comparison of the effect of chlorpromazine injected into the parietal vein and the effects of the drug on the respiratory responses.
injection is made into the femoral vein. The data in figure 1 indicate that the response is related to the concentration of the agent.

Feldman and Kidron (1) and Dasgupta and Hausler (2) have suggested that the respiratory stimulation following the administration of chlorpromazine may be due to the associated fall in arterial blood pressure. The fact that the fall in pressure occurs at about the same time tends to support this. The results shown in figure 2, however, do not uphold this opinion as the stimulation is still evident when the fall in arterial blood pressure is buffered. The respiratory inhibition also persists when the fall in arterial blood pressure is opposed. Concomitant with the decrease in arterial blood pressure there is a slight rise in central venous pressure, but it is unlikely that this is the cause of the respiratory inhibition as no such response occurs after giving other drugs which affect central venous pressure similarly. Also, a rise in central venous pressure is reported to be without effect upon respiration (4, 5). A further observation which tends to eliminate the fall in blood pressure as the stimulus for the respiratory responses is the fact that sinus denervation is without effect upon these responses while vagotomy alone eliminates the inhibition and greatly depresses the stimulation. It is improbable that aortic pressoreceptors but not sinus pressoreceptors would be involved. It is more reasonable to consider that a pulmonary chemoreflex is involved, possibly of the type discussed by Dawes and Comroe (6). The mild stimulation of respiration which sometimes persists even after sino-aortic denervation could be due to a pressure component as it has been demonstrated that following denervation some stimulation may occur in response to a fall in arterial blood pressure induced by hemorrhage (7) and certain vasodilator agents (8).

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REFERENCES