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ANALYSIS OF THE CENTRAL RESPIRATORY ACTION OF NALORPHINE IN DECEREBRATE DOGS

BY

FREDERICK F. KAO AND JULIUS BELFORD

From the State University of New York, College of Medicine at New York City, Department of Physiology and Pharmacology, Brooklyn, N.Y., U.S.A.

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Nalorphine has enjoyed widespread use as a counter measure in morphine-induced respiratory depression (Unna, 1943; Hart and McCawley, 1944). There is also convincing evidence that nalorphine can exert an ameliorating effect on respiratory depression induced in human beings by various barbiturates (Dulfano, Mack, and Segal, 1953), and can counteract depression of respiratory activity produced in experimental animals by pentobarbitone sodium or chloralose-urethane (Vivante and Kao, 1953; Belford and Kao, 1954; Vivante, Kao, and Belford, 1954), and other compounds (Costa and Bonnycastle, 1955). Thus, from the available evidence, it seems justifiable to postulate that nalorphine acts in such a way as to stimulate depressed respiratory centres* regardless of the depressant drug. Nalorphine also stimulates respiration in decerebrate dogs, and its site of action is not on the peripheral chemoreceptors (Vivante *et al.*, 1954).

A respiratory stimulant or depressant may act directly on the respiratory centres, or indirectly by changing the sensitivity of the centres to physiological stimuli, such as carbon dioxide tension. These effects may depend on, or be independent of, the molecular structure of the drug. It is the purpose of this paper to determine whether nalorphine operates through a direct stimulating action, or by sensitizing the respiratory centres, or by both mechanisms.

METHODS

Mongrel dogs of both sexes were used. Midbrain decerebration (Kao, Schlig, and Brooks, 1955) was performed under thiopentone sodium (25 mg./kg. i.v.) anaesthesia, supplemented, when necessary, with ether. A tracheal cannula was inserted and connected to a Douglas valve, the inlet of which was connected to a Douglas bag containing a CO_2-O_2 gas mixture and the outlet to a gasometer for measurement of the total ventilation. Respiratory rate was counted by observing the movement of the hand on the dial of the gasometer. Arterial blood samples were collected anaerobically from one femoral artery for both *p*H and plasma CO_2 determinations. The plasma total CO_2 was determined by means of a Van Slyke manometric apparatus, and the *p*H was measured with a Cambridge research-model *p*H meter using a water jacket (38° C.) microcondenser-type electrode. The P_{CO_2} was calculated from the Henderson-Hasselbalch equation.

A control period of 30 min. was allowed before the CO_2-O_2 mixture was given. After the ventilation had reached a steady state while the animal was breathing the CO_2-O_2 mixture, nalorphine (30 mg./kg. i.v.) was administered. Ten min. later the dog was given room air to breathe. Additional CO_2 inhalation experiments were performed on intact dogs anaesthetized with pentobarbitone sodium in an initial dose of 30 mg./kg. i.v., followed by smaller doses to produce deep respiratory depression.

RESULTS

The Respiratory Effect of CO_2 Inhalation in Dogs Anaesthetized with Pentobarbitone

The respiratory response of an anaesthetized dog to CO_2 inhalation is shown in Fig. 1, in which ventilation in l./min. BTPS (Committee on Nomenclature of Respiratory Physiology, 1950) is plotted as a function of time. At zero time, CO_2-O_2 mixtures were given. This figure shows that the same gas mixture did not necessarily initiate similar respiratory responses. This is better shown in Fig. 2, in which the response to CO_2 inhalation (5% CO_2 in O_2) is plotted against P_{CO_2} in mm. Hg. It is clear that in an anaesthetized dog ventilation was dependent on the level of anaesthesia. In deep anaesthesia the ventilation was less than during light anaesthesia. Correspondingly, the arterial P_{CO_2} was high during deep anaesthesia, as is to be expected during respiratory depression.

*The term respiratory centres as used here includes the central chemoreceptors which are sensitive to *p*H and P_{CO_2} and are located in the medullary tissue near the inspiratory and expiratory centres (Grodins, Gray, Schroeder, Norins, and Jones, 1954).

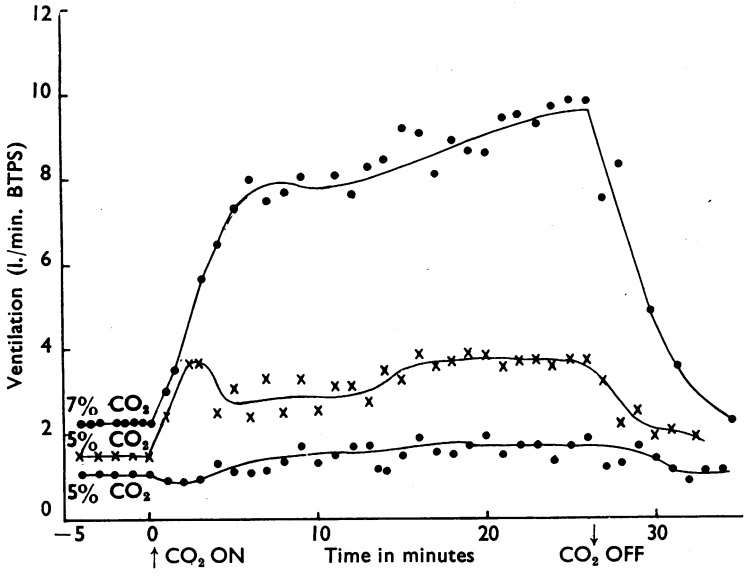

FIG. 1.—Dog, 9.3 kg., pentobarbitone anaesthesia; administration of 5% (1.15 p.m., bottom curve), 5% (2.15 p.m., middle curve) and 7% (3.15 p.m., top curve) CO_2 in the inspired air caused an increase of ventilation over the resting (30 min.) rate (only the last 5 min. of which is shown). Note: (a) no return to original resting value in each instance and (b) a similar but quantitatively different response to the administration of 5% CO_2.

The difference in response to the same percentage of CO_2 in the inspired air in an animal at different depths of anaesthesia is revealed by the different slopes of the family of lines in Fig. 2: the slopes were higher when anaesthesia was light, and vice versa. Another interesting point shown in Fig. 2 is that administration of a CO_2-O_2 mixture to a dog whose respiration is already deeply depressed by anaesthesia depresses respiration still further. This is to be expected, since a high concentration of O_2 was given with the CO_2, and such deeply anaesthetized dogs depend for the maintenance of their ventilation on the sensitivity of their peripheral receptors to O_2 lack.

It seems obvious from these observations that the sensitivity of the respiratory centres is affected by the level of anaesthesia. Hence the use of anaesthetized animals to test respiratory sensitivity to various agents is inadvisable. It is very difficult to maintain such animals at the same level of sensitivity. During anaesthesia the acid-base balance of dogs is dependent on respiratory activity, and the P_{CO_2} and the H^+ concentration of the arterial blood vary in the same direction (Fig. 3). Arterial puncture was carried out in one dog before anaesthesia, and it was found that the P_{CO_2} was 53.6 mm. Hg and the H^+ concentration was 38.5 mμM/l. After anaesthesia they were 70.5 and 51.9 respectively.

Similar observations were made on five anaesthetized dogs.

The Respiratory Effect of CO_2 Inhalation in Decerebrate Dogs

Eighteen tests were carried out in six decerebrate dogs to determine the sensitivity of their respiratory centres to CO_2 inhalation. The response of ventilation to CO_2 inhalation is shown in Fig. 4. Within the time of observation a reasonably steady state was attained. Fig. 5 shows the relation between ventilation and P_{CO_2} in mm. Hg during the steady state. A regression line (a) was fitted to the data, employing

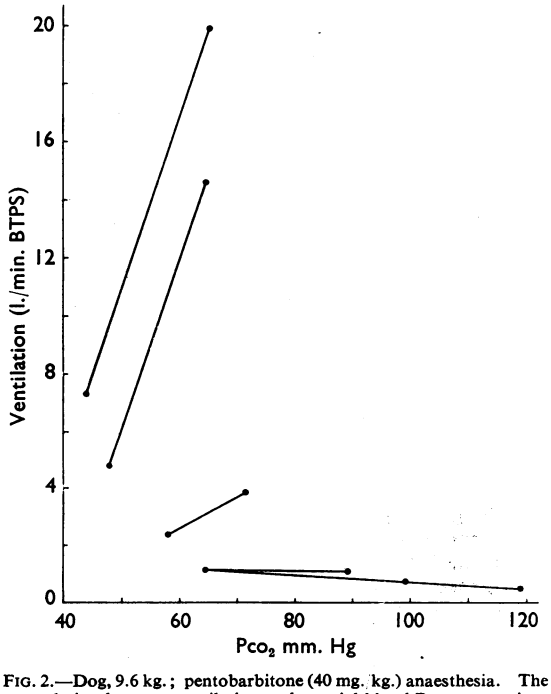

FIG. 2.—Dog, 9.6 kg.; pentobarbitone (40 mg./kg.) anaesthesia. The relation between ventilation and arterial blood P_{CO_2} at various depths of depression. The percentage (5%) of inhaled CO_2 did not vary. The slopes of the lines indicate the different sensitivity of the respiratory centres to CO_2 stimulation.

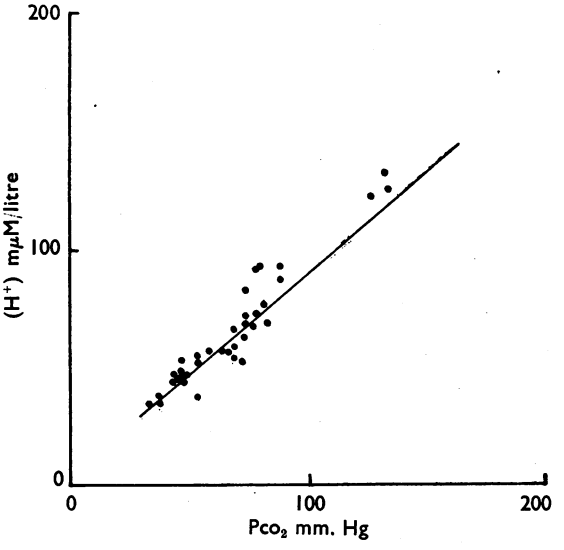

FIG. 3.—The steady-state relation between arterial blood H^+ concentration and P_{CO_2} in five dogs (36 determinations) anaesthetized with pentobarbitone.

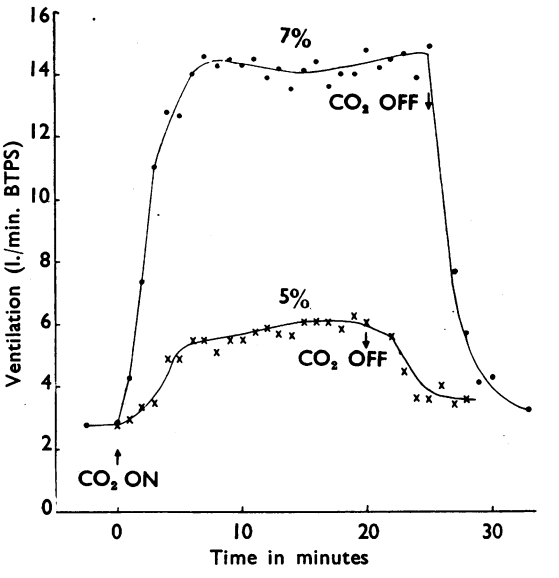

FIG. 4.—Dog, 8.2 kg. Decerebrate. Ventilatory response to 5% and 7% CO_2 inhalation. Note that the resting levels of ventilation returned to the same value between gas administrations.

an analysis of covariance (Snedecor, 1948), and it has the following equation:

Ventilation (l./min. BTPS) = 0.39 (± 0.08) P_{CO_2} mm. Hg − 10.32 (1)

with $r = 0.80$. Both the slope, 0.39, and the correlation coefficient, 0.80, are significant at the 1% level of probability. In contrast to the changes in sensitivity of the respiratory centres to CO_2 in the anaesthetized dogs, the respiratory centres of decerebrate dogs had a reasonably constant sensitivity.

The Effect of Nalorphine on the Respiratory Response to CO_2 Inhalation in Decerebrate Dogs

Thirteen tests were performed on five decerebrate dogs to investigate the effect of nalorphine on the sensitivity of the respiratory centres to CO_2 inhalation.

The ventilatory response to CO_2 inhalation and to nalorphine administration is shown in Fig. 6. CO_2 was given to this dog in the following sequence, 5%, 3%, and 7%. Nalorphine (30 mg./kg. i.v.) was administered after a steady state was reached in each instance. Fig. 6 shows that nalorphine apparently causes a similar response irrespective of the percentage of CO_2 inhaled. This statement is supported by the analysis of the data in Fig. 7, in which the ratio of the increments in ventilation after the first nalorphine administration to the ventilation after the subsequent nalorphine injection is plotted against the percentage of the inhaled CO_2. The regression line fitted to this group of data has a slope of 0.09 with an error of 0.13. That the slope does not significantly differ from zero indicates that the increase in ventilation after the injection of nalorphine is independent of the CO_2 administered.

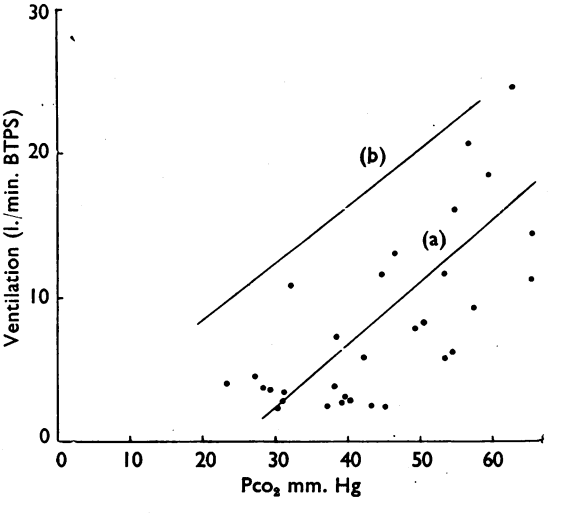

FIG. 5.—The relation between ventilation and P_{CO_2} in 6 decerebrate dogs during the steady-state condition of CO_2 inhalation (line (a) with dots). Line (b) represents the same relationship when in addition to CO_2 inhalation nalorphine was administered.

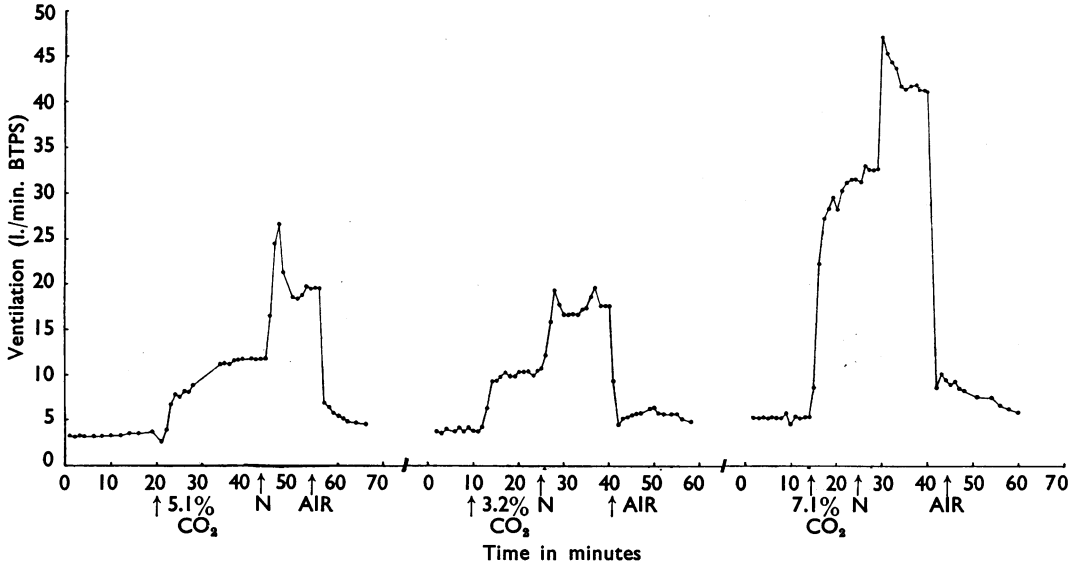

FIG. 6.—Dog, 13.6 kg. Decerebrate. Ventilatory responses to various CO_2 mixtures. At N nalorphine was administered. The animal was given room air to breathe at AIR. One hour elapsed between experiments. There is no statistical (*vide infra*, Fig. 7) difference in response to nalorphine when its administration is superimposed on each of the gas mixture inhalations.

Ventilation after nalorphine injection is plotted as a function of P_{CO_2} in mm. Hg (Fig. 5, line b). The slope of the line is 0.37 with $r=0.85$, and the complete equation expressing ventilation and P_{CO_2} is:

Ventilation (l./min. BTPS) = 0.37 (±0.18) P_{CO_2} mm. Hg + 0.45 (2)

The slope in this equation is significantly different from zero, but does not differ from the slope in equation (1) ($b=0.39$; $P>0.50$). In other words, the two lines expressed by equations 1 and 2 are parallel. This indicates that the sensitivity of the respiratory centres to CO_2 inhalation is not altered on the administration of nalorphine, and suggests that the nalorphine acts independently of changes in CO_2 tension.

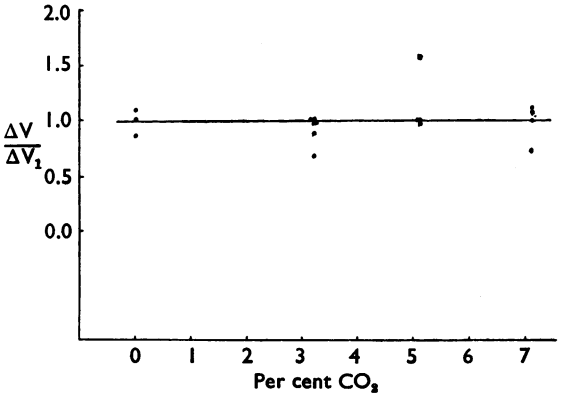

FIG. 7.—The relation between the ratio of the increments in ventilation after the first nalorphine administration to that after the subsequent nalorphine injections (with or without CO_2 inhalation) and the percentage of CO_2 in the inspired gas mixture. ΔV_1 = the increment of ventilation after the first injection of nalorphine. ΔV = the increment of ventilation after the succeeding injection of nalorphine. The line fitted to this group of data has a slope which is not significantly different from zero.

DISCUSSION

It seems appropriate to define the term sensitivity, since different authors may attach different meanings to it. If a stimulus is applied to a system and a response produced, the magnitude of the response is a function of two factors: (1) the magnitude of the stimulus and (2) the sensitivity of the system in question. If the sensitivity of a system is constant, the response plotted as a function of stimulus must be rectilinear. That is, the slope of the line expressing the relation between response and stimulus is constant. If, on the other hand, the slope changes, this implies that the sensitivity of the system is altered. The altered slope may be such that the whole line is shifted but is still rectilinear, or it may change according to the magnitude of the stimulus; in the latter event a curvilinear relation between response and stimulus would be expected. The curvature of the lines may increase or decrease according to the increase or decrease in the sensitivity of the system. Hence, the term sensitivity is here defined

as the magnitude of the change in response as a result of the change of the stimulus, or to express it symbolically:

$$\text{sensitivity} = \frac{\Delta R}{\Delta S}$$

where ΔR is the change in response and ΔS is the change in stimulus.

If in any particular situation a certain response is elicited after a stimulus is applied, and a definite sensitivity of the system is indicated, then upon adding another stimulus—as, for example, nalorphine during CO_2 inhalation—the change of sensitivity due to the second stimulus can be determined.

As the two lines in Fig. 5 are parallel, it is obvious that the respiratory centre was equally sensitive to CO_2 before and after nalorphine. The line expressing the relation between ventilation and P_{CO_2} after nalorphine injection is merely shifted upwards. It seems justifiable, therefore, to conclude that nalorphine does not change the sensitivity of the respiratory centres to CO_2 inhalation, but merely produces an additive effect. It may further be concluded that nalorphine has its own action, which is entirely independent of the carbon dioxide tension.

Summary

1. Dogs anaesthetized with pentobarbitone show respiratory acidosis, and the respiratory response to inhalation of CO_2 alters with the depth of anaesthesia.

2. The respiratory response to CO_2 inhalation is more constant in decerebrate dogs than in dogs anaesthetized with pentobarbitone. The relation between ventilation and arterial P_{CO_2} is expressed by a regression line which has a slope of 0.39.

3. In decerebrate dogs following administration of nalorphine in addition to CO_2, the relation between ventilation and arterial P_{CO_2} is expressed by a regression line which has a slope of 0.37; the latter is not significantly different from the value 0.39 ($P>0.50$).

4. It is concluded that nalorphine does not alter the sensitivity of the respiratory centres to CO_2 inhalation in decerebrate dogs. The mechanism of its respiratory stimulant activity is briefly discussed.

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