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DRUGS AND RESPIRATORY CONTROL

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Drugs and Respiratory Control

In the excellent review of this subject that appeared in the 1966 edition of this series (1) the material was restricted largely to effects of drugs on respiratory control. That practice will be continued in this review, largely omitting pulmonary circulation (2–10), metabolic functions of the lungs (11, 12), mechanical properties of the lungs (13–29), effects of O_2 at high pressure (30–37), and other aspects of pulmonary function (38). With few exceptions references will be to literature which has appeared since 1965, although selected references to older literature have been included where they are particularly pertinent.

In studying the effects of drugs on respiratory control the easiest, but usually not the most accurate, measurements are respiratory rate (f) and volume of air exhaled per minute (V_E) at rest, before and after exposure to the drug. Dividing minute volume by rate gives tidal volume (V_T), a measure of the amplitude or depth of breathing. These responses may also be measured with some constant or variable stimulus such as graded degrees of exercise, elevated levels of CO_2 or decreased levels of O_2 in the inspired air, or combinations of these. It is becoming common practice to determine CO_2 response curves of subjects as a measure of the effect of a drug (39–56). These response curves are usually determined with mixtures of CO_2 in O_2, thus keeping O_2 tension very high and largely eliminating peripheral chemoreceptor sensitivity to CO_2 or H^+ as a factor in the response (57–59). The slope and abscissa intercepts of these curves give two measures of central chemoreceptor sensitivity to the normal respiratory stimulant, CO_2. The former of these has been called the "transfer function" or "gain" and the latter the "detector" of the system (40). Drug effects on changes in response to respiratory forcing from low oxygen tension (58–61), exercise (62, 63), and combinations of these (58, 64–66) are much less common. Since CO_2 and H^+ stimulate both peripheral and central receptors while only the peripheral receptors are stimulated by low oxygen tension, additional information on drug action could be obtained by looking at the effect on the interaction of these agents. With facilities for supplying different gas mixtures to the subject, and instrumentation for recording end-tidal CO_2

and O_2 tensions, and minute volume of ventilation, it is possible to determine the CO_2 response curves at two or more oxygen tensions in a reasonable period of time.

Over a useful range the CO_2 response curve at any constant O_2 tension is a straight line and may be described by an equation of the form $V_E = S(P_{CO_2} - B)$, in which S is slope and B is intercept on the abscissa (67). Decreasing the O_2 tension changes S but not B. If the CO_2 response line is obtained at several O_2 tensions a "fan" of lines of different slope and common intercept is produced. A graph of slope against O_2 tension is an hyperbola describing the inverse relation between these variables. The equation for this curve contains three additional terms; (*a*) slope of CO_2 response line in complete absence of hypoxia (*b*) oxygen tension at which the slope is infinite and (*c*) a term describing the curvature of the hyperbola. This last term may be considered to be an expression of hypoxia sensitivity. Combining the two equations gives an expression for V_E in terms of alveolar O_2 tension (P_{AO_2}), alveolar CO_2 tension (P_{ACO_2}), and the three terms listed above plus the abscissa intercept. This approach has been described in detail by Cunningham & Lloyd (67, 68) and used to describe the respiratory stimulating effect of norepinephrine (69). The analysis indicated that the effect is primarily on the sensitivity to low oxygen tension. This would suggest that this agent should have little or no stimulating property in the presence of high oxygen tension; a prediction later verified (70).

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Normal Respiratory Gases

O_2 Insensitivity of high altitude natives.—This "parametric" approach has also been used to analyze the difference in response to low O_2 tension and increased CO_2 tension between native high altitude dwellers and sea level dwellers (71–73). It has been found that persons born at high altitude have a significantly depressed response to reduced O_2 tension compared with persons born at sea level (62, 72, 74–79), although the responses of the two groups to CO_2 are not markedly different (71, 73). This blunted response to low O_2 tension does not develop in sea level dwellers from extended sojourn at high altitude (75) nor does it disappear when native high altitude residents live at sea level for long periods (79). It appears that, in humans, chronic hypoxia during the early months of life results in irreversible loss of sensitivity of the peripheral chemoreceptors to low O_2 tension. This interpretation is supported by the fact that O_2 insensitivity is still present in patients after correction of Tetralogy of Fallot (80). In the limited studies that have been made it appears that this phenomenon is not exhibited in animals (60, 81, 82).

Oscillating versus steady stimulus.—The theory proposed by Yamamota (83) that CO_2 receptors, presumably arterial chemoreceptors, respond more briskly to an oscillating than to a steady signal of the same mean strength has received renewed attention over the past few years. Attempts to demonstrate an increased response in humans have been largely unsuccessful (84),

however the enhanced response in subjects breathing through an added external dead space (tube-breathing) suggests that the shape of the CO_2 tension profile during the respiratory cycle is important in determining the response of the peripheral chemoreceptors to CO_2 when the sensitivity is amplified by low O_2 tension (85–87). Semple and co-workers have devised a recording pH electrode with which they have demonstrated respiratory oscillations in arterial blood pH in the cat (88, 89) and an alteration in the shape of the oscillation pattern with tube breathing (89). A fast responding O_2 electrode has also recorded O_2 tension variations of 1 to 4 torr in arterial blood which were synchronous with ventilation (90). A direct approach by perfusing the carotid sinus areas in dogs has demonstrated that an added stimulus above that expected from the level of the CO_2 tension is provided when the rate of increase is rapid (91, 92). If the rate of rise exceeded 10 torr/second, ventilation exceeded that produced by a steady CO_2 tension of the same value (93). Similar experiments in which the vertebral arteries of dogs were perfused indicate that it is the peripheral receptors that dominate in response to rapid transients (94).

Because of the negative feedback in the $V_E - P_{CO_2}$ relationship it is difficult or impossible to impose a particular alveolar or arterial blood CO_2 tension profile in mammals since the respiratory response alters the profile. This feedback loop can be opened in the chicken by puncturing the air sacs and ventilating the animal by a constant flow-through of gas (95). Using this technique a sinusoidal pattern of CO_2 tensions did not produce an increase in ventilation with normal or high O_2 tensions (96). The effect of oscillating CO_2 tension at low O_2 tension has not been reported in this preparation.

Vagal afferents and response to CO_2.—Normal individuals who have breathed 10% CO_2 or higher commonly report a feeling of distress accompanying the vigorous respiratory effort produced by this intense stimulus. Experiments in which conscious subjects have been paralyzed with tubocurarine (97, 98) or who have had bilateral block of vagus and glossopharyngeal nerves (99) make it clear that the tolerable limit of CO_2 is markedly affected by impulses from the lungs and chest wall. Breath holding in paralyzed subjects (with O_2 tension kept above 300 torr) did not produce discomfort with CO_2 tensions increasing to high values. The subject with blocked vagus and glossopharyngeal nerves rebreathed a 7% CO_2 mixture without discomfort. The CO_2 response curve of this subject during the nerve block was considerably depressed in slope with no change in intercept. Since the very high O_2 tension used in these experiments "chemically deafferentates" the carotid bodies, the effect is considered to be mediated by the vagus. Other experiments on humans have demonstrated that tolerance to CO_2 is influenced by the lung volume and tidal volume at which the breathing is carried out (100). Subjects working at 4 atmospheres absolute pressure had alveolar CO_2 tensions above 70 torr without experiencing discomfort (101). The only subject who showed discomfort was one

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who hyperventilated to keep his CO_2 tension down to 54 torr. He suffered from dyspnea and exhaustion.

Experiments with animals (102, 103) support the contention that impulses mediated by the lungs play an important role in determining the respiratory responses to CO_2.

Carbon dioxide.—In contrast to the depressed response to CO_2, as evidenced by a shift to the right and a decrease in slope of the $V_E - P_{CO_2}$ lines, in subjects chronically exposed to increased CO_2 tension (104, 105); one subject intermittently exposed to 3% CO_2 15 hours each day for six days demonstrated an increase in response to 5% CO_2 (106).

CO_2 response curves in adult heart disease patients with Cheyne-Stokes breathing were shifted to the left and decreased in slope, compared with curves of normally breathing heart disease patients (107), however the most striking difference between the two groups was the prolonged circulation time in the Cheyne-Stokes patients. In premature infants, CO_2 sensitivity does not appear to be a factor in the etiology of periodic breathing (108).

In hypothermic dogs the depressed response to CO_2 was present in the presence of high oxygen tension (64). This is interpreted as evidence that the depressant effect is exerted primarily at the central receptors. The hypothermic animal might be a good preparation for testing the effect of drugs on central receptor sensitivity to CO_2.

The hypothesis that CO_2 chemoreceptors should be located on the venous side of the circulation was not supported by results on cats in which vena cava blood was diverted through a homologous lung ventilated with 100% CO_2 (109).

Although CO_2, or the H^+ produced by increasing CO_2 tension, is the most potent chemical respiratory stimulant known; it is considered to be a depressant to respiration, an anesthetic, and a convulsant at very high concentrations (1). Recordings from the phrenic nerve in anesthetized or decerebrate cats indicate that inspiratory activity increases with increasing CO_2 tension, becoming so intense with 40 and 60% CO_2 that the expiratory phase was compromised and tidal exchange ceased (110). In dogs lightly anesthetized with thiopental sodium and maintained with 30% CO_2 or anesthetized directly with 30% CO_2, spontaneous respiration was maintained until inspired CO_2 was 55 to 65%. Ventilation on 30% CO_2 was less than the maximal that can be produced by CO_2 but still well above normal (111). In these experiments convulsions were never observed during CO_2 breathing but were fairly common in the immediate posthypercapnic period (112, also Brown, E. B., Jr. & F. A. Miller unpublished observations).

CO_2 or H^+?—Results consistent with the hypothesis that H^+ is the stimulus for both peripheral and central chemoreceptors have been obtained on humans (113) and animals (114). Both cerebral blood flow and V_E were a single linear function of CSF pH in both metabolic acidosis and alkalosis

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in humans (113). Perfusion of the carotid sinus area with solutions of varying CO_2 tension and HCO_3^- concentration in cats, indicated that the receptors in this area are sensitive to H^+ and are separated from the vascular space by a barrier more permeable to CO_2 than to HCO_3^- (114).

Oxygen.—The precise mechanism by which low O_2 tension stimulates the peripheral chemoreceptors continues to be elusive (115). The rate of delivery of O_2 to the receptor cells as well as its tension in arterial blood appears to influence the respiratory response (116). The rate of delivery of O_2 must influence the tension at intracellular sites in O_2 consuming cells.

The role of the arterial chemoreceptors was the subject of a symposium in 1966. The proceedings of that meeting (117) review the status of the field at that time.

Posthyperventilation apnea in the pentobarbital sodium anesthetized dog may continue until arterial O_2 tension falls to 35 torr (118). It is not surprising that the anesthetized animal might not respond normally to decreased O_2 tension, however unanesthetized dogs also exhibited posthyperventilation apnea even in the presence of metabolic acidosis produced by NH_4Cl ingestion (119). It appears that this phenomenon is elicited more readily in the dog than in man.

Anesthetics

The mechanisms involved in depression of respiration by anesthetics were analyzed in the previous review (1). Other reviews were cited to which now should be added the review on effects of anesthetics on respiration by Dobkin & Grogona (120). These authors include the broad spectrum of anesthetic agents, dividing them into several groups. It would be redundant to go into this subject here; rather, references will be made to very recent investigations in this field.

Human studies.—The respiratory effects of halothane continue to be the subject of studies (43) in which this agent, usually in combination with N_2O, is compared with other anesthetics (42, 121, 122). Munson & Larson (43) illustrate the effects of halothane as successively depressing the slope of the $V_E - P_{CO_2}$ response curve as the concentration of halothane increases from 0 to 2%. Addition of N_2O to halothane increased resting arterial blood P_{CO_2}, but had no effect on the $V_E - P_{CO_2}$ relation (41). In a comparison of three agents at equipotent anesthetic concentrations, halothane and fluoroxene were more potent respiratory depressants than cyclopropane (42). Fluroxene depressed the slope and shifted the CO_2 response lines to the right as the concentration increased to 2.5 times the minimum anesthetic concentration (MAC) (42).

Methoxyflurane depressed the slope of the $V_E - P_{CO_2}$ response curve in proportion to dose (39). In a comparative study with diethyl ether, a concentration of 5.6% of ether, equal to 2.9 MAC, was reached before resting

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ventilation was depressed and arterial blood CO_2 tension (P_{ACO_2}) increased (123). By contrast methoxyflurane produced an early and progressive increase in P_{ACO_2} with increasing concentration of the agent.

Animal studies.—Other anesthetics studied were pentobarbital (40, 124–126), methohexital (127), thiopental (127), and teflurane (128) in dogs; urethane and chloralose in cats (40); and phencyclidine in monkeys (129).

Local Anesthetics

The respiratory effects in man of intravenous infusions of mepivacaine and lidocaine have been studied at a dose level of 5 mg/kg body weight administered over a period of 20 minutes. No significant changes in P_{ACO_2}, arterial blood pH, or O_2 saturation were observed (130, 131). When intravenous procaine and lidocaine were added to 0.7 mg/kg of succinylcholine, the duration of apnea was prolonged (132).

Ethanol injected into the CSF of cats decreased the slope of the V_E–log P_{CO_2} response lines without changing the CO_2 threshold value (44). Procaine administered by the same route decreased the slope and increased the threshold value. The effects are interpreted as centrally mediated and largely unaffected by peripheral chemoreceptor input.

Narcotic Analgesics

Recent references to the effects of narcotic analgesics on respiratory control are listed in Table 1. Morphine continues to be the standard by which the respiratory effects of other drugs are judged (133–137) and studies on

TABLE 1. Central Depressants

Agent	Reference
Narcotic Analgesics	
Morphine	
In man	42, 46, 54, 56, 140, 148
In animals	133, 139, 141, 146, 149, 150
Meperidine	49, 50, 135, 142, 143, 151, 152
Codeine	45, 46, 150, 153, 154
Fentanyl	55, 135, 144, 155–157
M183	134
Morphine-N-oxide	147
Etorphine (M99)	136, 147
Alpha-Prodine	137
Piritramide	158
Narcotic Antagonists	
Nalorphine	54, 149, 150
Pentazocine	47, 48, 159–163

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morphine itself continue to appear (54, 56, 138–140). Intravenous injections of morphine in eight healthy subjects produced the usual respiratory depression in six and an unusual stimulation of respiration in the other two (138). The increase in V_E lowered end tidal P_{CO_2} from 39.5 to 30 torr in ten minutes. The subjects reported that the subjective sensation was simply a desire to hyperventilate (138). After seven weeks of morphine dependence in humans, CO_2 sensitivity, which was decreased early in the cycle as evidenced by the $V_E - P_{CO_2}$ curves being shifted to the right, returned to normal (56). During withdrawal the subjects were hypersensitive to CO_2.

Although morphine acts centrally (140), intravenous injection causes a more rapid respiratory response than does injection into the third or fourth ventricle (141). In this study an unexplained stimulation of breathing followed injection into the bulbar subarachnoid space.

The respiratory depressant effects of meperidine are not significantly altered by combinations with tranquilizers (50, 142) or narcotic antagonists (143). In equianalgesic doses with meperidine and morphine, the short acting drug, fentanyl, is equally as depressive to respiration (135, 144). The respiratory depressant action of Innovar, a combination of fentanyl and droperidol, is due to the presence of fentanyl (55). References to studies of other combinations of drugs with fentanyl are included in Table 1.

The extremely potent etorphine and related thebaine derivatives are at least as depressant to respiration as morphine in equianalgesic doses (133, 134, 136, 145–147).

Narcotic antagonists.—The mechanism of action of nalorphine in antagonizing the respiratory depression of morphine was reviewed previously (1). Pentazocine is a similar agent with similar action. It has analgesic properties approximately equal to those of meperidine on a milligram for milligram basis (159), has less respiratory effect than meperidine (47) or morphine (48, 160, 161), and has been recommended as a useful drug for pain in myocardial infarction (164). A difference between the respiratory effects of the d and l isomers of pentazocine has been reported (162). Naloxone appears to be an effective antagonist of pentazocine (163).

Drugs that Stimulate Respiration

The action of CO_2 and O_2 as controlling factors in regulation of breathing have been reviewed earlier. In this section references will be given to studies that have been made of other agents that act to stimulate respiration. These are listed in Table 2.

Hydrogen ion.—The respiratory response to increased extracellular H^+ produced by infusion of HCl is much stronger in adult dogs than in very young pups (165). The explanation for this difference is not available.

It has been assumed that NH_4Cl stimulates respiration by decreasing extracellular fluid pH, in a manner wholly analogous to HCl infusion (167).

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TABLE 2. DRUGS THAT STIMULATE RESPIRATION

Agent	Reference
Inorganic Ions	
H^+	165, 166
NH_4CL	167, 168
$NaHCO_3$	169–171
K^+	172, 173
Ca^{++}	174
Cyanide	175, 176
Salicylates	177
Carbon Monoxide	178
Analeptics	
Doxapram	179–182
Bemegride	181, 183
Dimefline	184
Nikethamide	181, 183–185
Prethcamide	184, 185
Vanillic acid diethylamide	183, 186
Taloximine	183, 187
Piperidinomethylcyclohexane	188
Humoral Agents	
Epinephrine	189–195
Norepinephrine	69, 70, 189, 195, 196
Acetylcholine	197

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Results obtained with intravenous infusion of NH_4Cl suggest that the increase in V_E is due to release of sympathomimetic amines since adrenalectomy or the drug, pronethalol, block the effect (168).

Buffers.—Although both $NaHCO_3$ and the organic buffer, tris (hydroxymethyl) aminomethane, commonly known as THAM, increase blood pH (169), the immediate effect on respiration produced by intravenous infusion of the two drugs is completely different. THAM effectively neutralizes H_2CO_3 by combining to form the bicarbonate thereby reducing CO_2 tension, increasing HCO_3^-, and increasing pH. Conversely, infusion of $NaHCO_3$ into a well buffered, relatively acid extracellular fluid results in release of CO_2, and elevation of CO_2 tension, pH, and HCO_3^- (170, 171). In both cases blood pH becomes more alkaline, however the immediate respiratory effects are opposite (169). The explanation is in the effect on intracellular pH in the two cases. With THAM, intracellular pH should increase as P_{CO_2} decreases. Because CO_2 moves across cell wall barriers much more rapidly than the HCO_3^- ion, early in $NaHCO_3$ infusion intracellular pH falls while extracellular pH is rising (198, 199). During this phase V_E increases; only

later when sufficient HCO_3^- has moved into the cell to increase intracellular pH or when HCO_3^- infusion has terminated and P_{CO_2} has decreased does V_E decrease as would be expected with metabolic alkalosis (171). Recent evidence suggests that the barrier to HCO_3^- transport into cells is not as rigid as we had formerly thought (200), nevertheless during the early stages of $NaHCO_3$ infusion respiration is stimulated.

Potassium ion.—Cameron (172) has suggested that K^+ may be the important variable in regulating respiration. Liu, Huggins & Hoff (173) have demonstrated that receptors in the isolated perfused leg, which by way of impulses over the femoral nerve increase respiration, can be stimulated by increased K^+ concentration in the perfusate. Propranolol and phenoxybenzamine acting centrally block the respiratory response.

Analeptics.—Mechanically assisted respiration and good supportive care (10) have largely replaced the need for drugs that stimulate respiration in patients with acute respiratory insufficiency. Even so the search for effective and specific drugs that stimulate breathing continues (181). Doxapram has shown promise in animals (180, 182) and on human volunteers (179). Taloximine antagonized the depressant action of morphine and sodium pentobarbital in animals (183, 187).

Humoral agents.—The influence of pH on the cardiovascular effects of the sympathomimetic drugs is well known. An effect of pH on the respiratory stimulating action of these agents has also been observed, although the results are not entirely consistent (193, 194).

Carbonic anhydrase inhibitors.—The physiological action of these compounds has been reviewed previously (1, 201). Since one aspect of acclimatization to high altitude is increased excretion of HCO_3^- by the kidneys, and since carbonic anhydrase also produces renal HCO_3^- excretion, acetazolamide and benzolamide have been compared for their effect on this process (202). If reduction of plasma HCO_3^- is an indicated goal in therapy of patients with chronic obstructive lung disease, carbonic anhydrase inhibitors will accomplish the desired end (203). The advantage of the carbonic anhydrase inhibitor, dichlorphenamide, over NH_4Cl for this purpose was questionable (204). Dichlorphenamide did result in some improvement in arterial blood O_2 saturation, apparently due to decreased CO_2 tension, in patients suffering from chronic respiratory insufficiency during graded levels of work (205, 206).

Acetazolamide has been used to treat Cheyne-Stokes respiration with limited success (207).

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