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The Neuropharmacology of Respiratory Control

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I. Introduction

HISTORICALLY the development of analeptic or respiratory stimulant drugs was almost abolished with the introduction of reliable mechanical ventilatory devices. However, the large number of persons with chronic com-

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pensated respiratory insufficiency could never be managed with mechanical assistance. If more specific and less toxic drugs could be found to stimulate respiration, perhaps some of the morbidity and mortality associated with several respiratory failure syndromes could be reduced.

The majority of information on the central control of respiration has been provided by neurophysiological studies of the cell groups whose firing rate is altered as a function of the respiratory cycle. Regardless of the sophistication in understanding the anatomy, neurophysiology, and neuropharmacology of respiratory control, pharmacological intervention in patients with pathological respiratory control states will more likely be accomplished via parenteral drug administration rather than by stimulation or ablation of the nervous system. Despite the considerable emphasis on the location, connections, and electrophysiological properties of respiratory related neurons, it is in recent years only that basic information concerning the neurochemical control of respiration has begun to develop. In fact, much of what has been learned is inferential from drug-induced perturbations of respiratory function. The investigation of central neurochemical control systems has recently contributed greatly to our understanding of the central control of the cardiovascular system (306). In addition, the pharmacotherapy of mental disease has been tremendously aided by the expansion of information concerning the action of drugs on central monoamine and other neuronal systems. It is obvious, however, that in neither cardiovascular nor behavioral pharmacology do we possess the degree of anatomical localization of central control that already exists for respiration. This may account for the development of research on respiratory control as an area of neurophysiology rather than of neuropharmacology. Therefore, it is believed that increased knowledge of the neurochemical basis of respiratory function will increase the likelihood of improving pharmacological interventions in pathological states of respiratory control.

This review will focus on recent developments demonstrating how drugs can influence respiration via interactions with putative CNS neurotransmitter mechanisms. Thus, not all drugs that affect respiration are mentioned. Our primary goal is to relate these drug studies to other background knowledge of anatomy and physiology of respiration in order to provide a framework upon which new drugs can be developed to aid in management of patients with respiratory failure.

II. Respiratory Control

The present summary seeks to briefly review only the relevant anatomy and physiology of respiratory control. Other reviews should be consulted for a comprehensive consideration of these areas (22, 302, 361).

The control of ventilation is classically described as a series of feedback loops that attempt to keep arterial CO_2 and O_2 tensions constant (fig. 1, designated RPG). The central CO_2 sensing and responding mechanism is located in the medullary reticular formation near the ventral surface of the medulla (H in fig. 1). In addition, however, there are peripheral CO_2 sensitive sites in the carotid bodies and indeed the pulmonary parenchyma itself, although the contribution of these sensing sites seems small (92). In any case, it is probably locally induced changes in H^+ that are ultimately responsible for altered signal generation, not CO_2 itself [for review, see Dempsey and Forster (92)]. The O_2 tension is sensed peripherally at the carotid and aortic bodies, with impulses transmitted centrally over the 9th and 10th cranial nerves to the CNS for signal processing (F, fig. 1). The basic rhythmicity or oscillation pattern that controls or is closely linked to respiratory frequency is located in the medulla-pons region (22, 117, 158, 304, 361). However, the respiratory pattern can become irregular and minute ventilation can change as known afferents (9th and 10th cranial nerves, hypothalamus, higher tegmental reticular formation neurons, spinal cord afferents, etc.) are transected or removed.

There are three groups of neurons in the medulla whose frequency of firing is correlated with the respiratory cycle; this indirectly implies some relevance to respiratory timing (see figs. 2–4). The nucleus ambiguus cells of the ventral respiratory neurons are active most probably because of their innervation of the accessory respiratory muscles (227) and hence cannot be the source of respiratory cycle development. Either of the other major groups, the ventral respiratory neurons, nucleus retroambiguus (RA), or the dorsal respiratory neurons, represented by the ventrolateral cell groups of the nucleus tractus solutarius (NTS), could be the "pace setter" or source of respiratory rhythmicity. However, since the RA neurons do not innervate the NTS and the NTS neurons have been shown to project to the RA region, the best candidate is the NTS. This matter is unresolved, and the basic respiratory rhythm-generating neurons have not yet been certainly located. For this reason, in figure 1, the RPG is diagrammed as a separate entity from the above anatomical groups, when in fact, all three groups described in more detail below may be part of the ultimate determinate of respiratory drive.

A. Dorsal Respiratory Neurons

Ventrolateral to the NTS is the dorsal group of respiratory neurons which are basically of two types. About one-half, designated Rβ, can be monosynaptically or oligosynaptically affected by vagal nerve stimulation (the Hering-Breuer reflex, (F. (fig. 1)), whereas Rα cells, which like Rβ fire largely during the inspiratory phase of respiration, do not receive direct vagal input (339) (see fig. 2). These neurons project to both the motor neurons within the spinal cord, which innervate the diaphragm and intercostal muscles, and to cells in the ventral respiratory cell group (largely RA) where they could interact with these other neurons whose firing rate also varies with the respiratory cycle.

Wyman (361) has proposed that the termination of the inspiratory firing phase in the NTS could be brought about by a combination of: a) some intrinsic phasic nerve activity of these NTS cells, perhaps related to their rate of firing; b) the result of direct vagal inhibition afferents (lung volume-dependent stretch receptors that send afferent impulses in the vagus nerves to inhibit inspiration—the Hering-Breuer reflex) (G, fig. 1); or c) the result of inhibitory impulses from elsewhere in the brain, such as the pneumotaxic center or nucleus parabrachialis medialis (NPBM) (118, 341) (I, fig. 1). Thus, drugs could exert effects on respiratory frequency or tidal volume by either directly or indirectly affecting inspiratory termination.

B. Vagal Influence

The Hering-Breuer reflex terminates the increasing nerve discharge of respiratory NTS cells that produce inspiratory muscle activity. Although previously thought to be an all or none response (39) [i.e. inspiration is not slowed, simply terminated completely, or not affected (G, fig. 1)], recent evidence (367) suggests substantial integration and processing of inspiration-terminating vagal inputs. To terminate inspiration early, a much larger volume of lung inflation, and presumably receptor activation, is required than is necessary later in inspiration when a smaller volume of inflation will suffice. Therefore, a central inhibiting circuit must be activated during inspiration and this circuit alone becomes sufficient to terminate inspiration in animals treated by vagotomy. In normal animals, summation of this inhibiting circuit with vagal impulses presumably occurs (143, 361). The exposure to CO_2 increases the rate of increase in phrenic nerve discharge, whereas an elastic load that resists lung expansion prolongs the duration of phrenic discharge without altering the rate of inspiratory phrenic nerve discharge. Both perturbations are associated with increased muscle activity, and will produce a more rapid turning off of inspiration (143). Pulmonary stretch receptors of the rabbit are also sensitive to CO_2 (246), but no similar information is available for the rat. Thus, a portion of the increased tidal volumes produced by CO_2 exposure could be secondary to a decreased stretch receptor afferent stimulation. Pulmonary J receptors are sensitive to some chemicals such as phenyldiquanide and capsaicin, which slow respiration or produce apnea (22) after intravenous administration. These drugs seem to act by altering vagal afferent impulses (F, G, fig. 1).

C. Nucleus Parabrachialis Medialis

The collection of neurons in the region of the medial and lateral parabrachial nuclei (NPBM) could also be a site of drug-induced changes in inspiration (I in fig. 1 and figs. 3,4). These neurons show a tonic firing rate when the vagus nerves are intact, but begin to cycle with the slow deep respiratory cycle that develops when the vagal nerves are divided (340). Some investigations have indeed described oligosynaptic, presynaptic interactions of vagal afferent impulses with these neurons. If, after cutting the vagi, these pontine neurons are also ablated, the respiratory pattern changes to apneustic breathing in which the inspiratory phase is markedly prolonged. Stimulation of this nucleus, in fact, terminated inspiration prematurely, which suggests that these nerves may also control respiratory timing (118).

Since transection of the brain stem posterior to the NPBM usually produces a rhythmic respiratory pattern that is little altered by vagotomy (345), it would seem that vagal afferents may also inhibit inspiration after initial synaptic contact with some pontine structures. Phasic stimulation of neuronal structures in the pneumotaxic center, i.e., the NPBM or Kölliker-Fuse nucleus in the cat, entrains the respiratory pattern and can prematurely terminate the inspiratory phase; these nuclei assume a phasic firing pattern when pulmonary afferent impulses are removed after vagotomy (118). In fact, in man the pulmonary vagal afferent system may be less important than wholly centrally located inhibitory systems which terminate inspiratory effort. These results in man are contrary to many studies in animals [see Berger et al. (22) for references] in which high pontine lesions and vagotomy do not produce apneustic breathing patterns until anesthesia is induced, which suggests that areas outside the rhombencephalon can exert important respiratory effects (K, fig. 1). In addition, vagotomy or lesions of the rostral pons in decerebrate cats can produce prolonged inspiratory activity (apneusis) when combined with ventrolateral cervical cord lesions (C, fig. 1), which again suggests that peripheral impulses from other parts of the body may contribute to the cessation of inspiration (195,288) and the start of expiration.

Since periodic phrenic nerve activity does persist after removal of the vagi and NPBM, an even simpler cycling pattern generator may exist in the medulla (192) (J, fig. 1). Several workers have described the presence of neurons throughout the reticular formation from the brain stem to the basal diencephalon (336) that fire in a pattern related to respiratory rate. Furthermore, respiration can be altered voluntarily, reflexly in response to changes in mechanical properties of the thorax, eating, coughing, and in response to changes in metabolic rate, exercise, temperature, and many other circumstances (22, 361). It is, thus, apparent that more diffuse, obviously less well localized neuronal activities also modulate respiratory activity. (289).

D. Ventral Respiratory Neurons

The ventral respiratory group of cells that influence respiration are located in the RA and nearby areas. They fire in relation to the respiratory cycle, but may fire during either inspiration, expiration, or both (in figs. 1 and 2). The RA has been thought to be involved in shaping motor output important to respiration (227, 235). For many years, it was thought that the basic respiratory

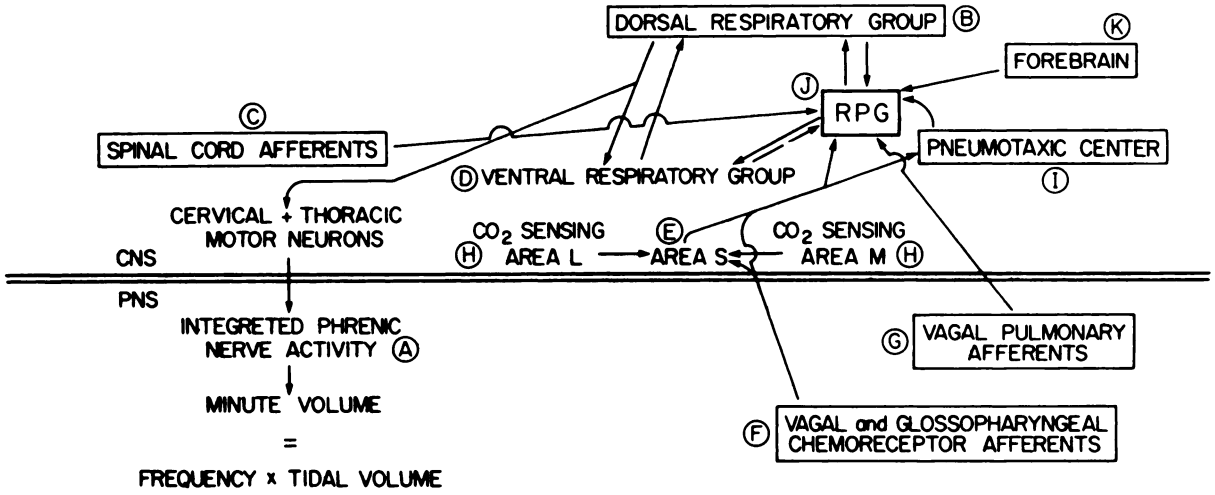

FIG. 1. Diagram of possible sites at which drugs may alter respiratory activity. RPG, respiratory pattern generator.

Abbreviations

AMB, Nucleus ambiguus
BC, Brachium conjunctivum
BP, Brachium pontis
C, Nucleus cuneatus
CP, Cerebral peduncle
CS, Nucleus centralis superior
CU, Nucleus cuneiformis
DB, Decussation of the brachium conjunctivum
DS, Nucleus tegmenti pedunculopontinus, subnucleus dissipatus
FL, Fasciculus longitudinalis medialis
G, Nucleus gracilis
GCM, Griseum centrale mesencephali
GCP, Griseum Central pontis
GP, Griseum pontis
IC, Inferior colliculus
IP, Nucleus interpeduncularis
KF, Kölliker-Fuse nucleus
LC, Locus nucleus coeruleus
LI, Nucleus linearis intermedius
LLD, Nucleus lemnisci lateralis dorsalis
LLV, Nucleus lemnisci lateralis ventralis
LRM, Nucleus lateralis reticularis, subnucleus magnocellularis
LRP, Nucleus lateralis reticularis, subnucleus parvocellularis
MD, Medullary (pyramid) decussation
ML, Medial lemniscus
n VII, Nucleus of the facial nerve
n XII, Nucleus of the hypoglossal nerve
NTS, Nucleus tractus solitarius
OI, Inferior olivary complex
OSL, Superior olivary nucleus, lateral part
OSM, Superior olivary nucleus, medial part
P, Pyramidal tract
PBL, Nucleus parabrachialis lateralis
PBM, Nucleus parabrachialis medialis
POO, Nucleus pontis centralis oralis
RA, Nucleus retroambiguus
RB, Restiform body
RD, Nucleus raphe dorsalis
RM, Nucleus raphe magnus
ROB, Nucleus raphe obscurus
RPA, Nucleus raphe pallidus
RPO, Nucleus raphe pontis
RTP, Nucleus reticularis tegmenti pontis
SU, Nucleus subcoeruleus
TC, Corticospinal tract
TL, Nucleus trapezoidalis lateralis
TM, Nucleus trapezoidalis medialis
TV, Nucleus trapezoidalis ventralis
TST, Nucleus tractus spinalis nervi trigemini
Vme, Mesencephalic tract of the trigeminal nerve
VII, Facial nerve root fibers
X, Nucleus of the vagus nerve
XII, Hypoglossal nerve root fibers

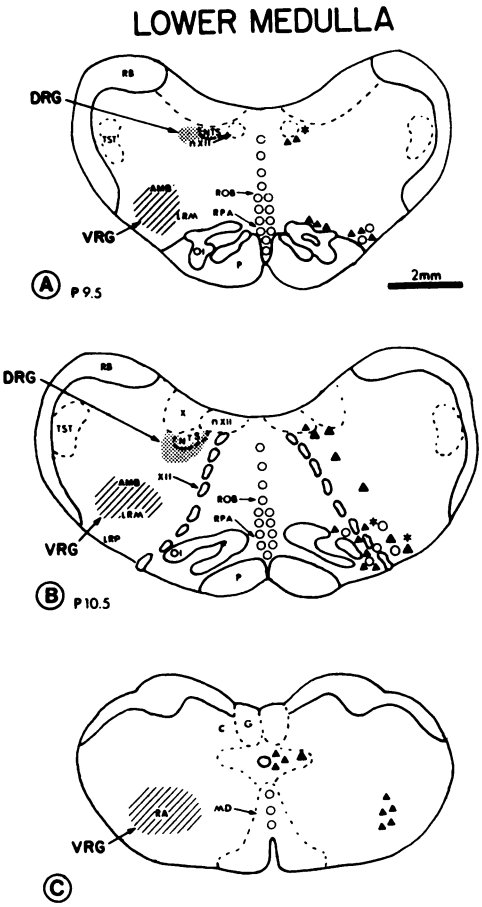

FIG. 2

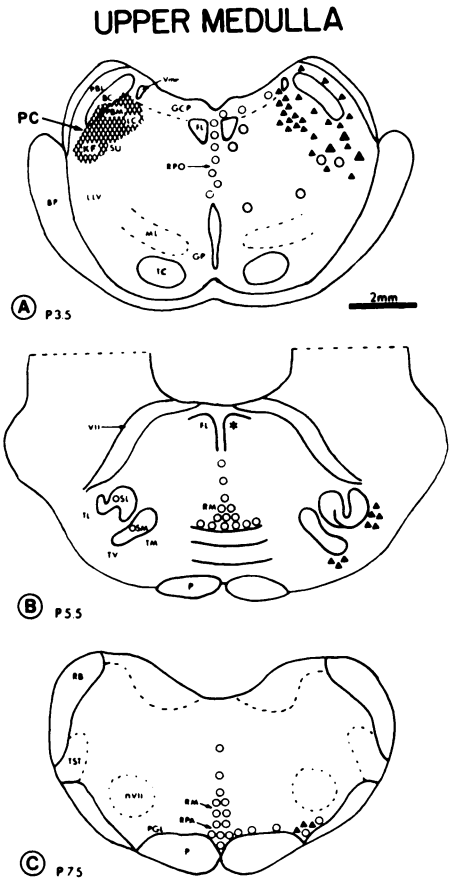

FIG. 3

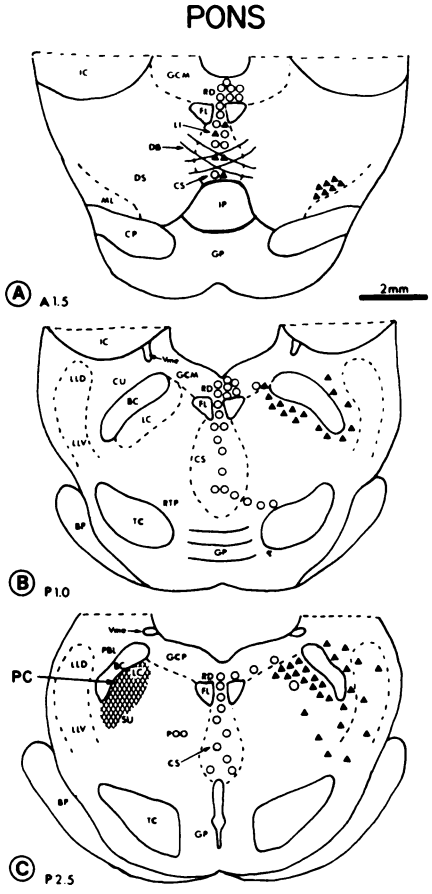

FIG. 4

FIGS. 2–4. These figures are traced from diagrams published by Poitras and Parent (277); however, they have been slightly modified to include the findings of Lackner (197). Anatomical diagrams are of coronal sections with location given according to the atlas of Snider and Niemer (317); sections are arranged in rostral-caudal order (A to C on each figure). ▲, catecholamine fluorescent cell bodies; ○, serotonin containing cells. Also, since we are aware of no studies of phenylethanolamine N-methyltransferase positive cell bodies in the cat, probable locations of these neurons (174) have also been indicated by these diagrams. Abbreviations indicate major anatomical structures and shaded areas indicate areas of importance in respiratory timing: diagonal lines, ventral respiratory group; cross-hatched areas, pneumotaxic center; dotted areas, dorsal respiratory group.

rhythmicity was generated by a simple, mutually inhibiting neuronal balance between those neurons which fire during inspiration (RA and NTS) and which simultaneously inhibit neurons which fire during expiration (largely RA) and vice versa during expiration (295). This simplistic concept was placed in doubt by subsequent work which could not find anatomical or physiological evidence directly linking the expiratory firing neurons of the ventral respiratory neurons with simultaneous inhibition of inspiratory neurons (227). Thus, many neurophysiologists interested in respiratory timing have searched elsewhere for the fundamental pacemaker (J, in fig. 1). More recently, however, Richter et al. (289) have developed a rational explanation of why such interactions would be hard to demonstrate even though they exist, and in fact they presented some data which suggested that they do occur.

The ventral surface of the medulla and structures immediately deep to this region, medial to the 12th cranial nerve exit from brain stem, are also relevant to a review of drug effects on respiratory control. These areas are concerned with sensitivity to local H^+ concentrations, which vary as a function of CO_2 tension. From the work of Loeschcke et al. and Mitchell et al. it is known that the CO_2 sensitive areas are probably located just beneath the ventral surface of the medulla, and consist of caudal (L) and cephalic (M) sensory (ultimately to extracellular H^+) (H in fig. 1) zones and a middle integrating or processing center (S) (127, 227, 236, 302, 303)) (E, fig. 1). Coagulation of the integration area (S) between the two sensing areas leads to a sharp decrease of breathing ($PaCO_2$, 63 torr in anesthetized cats). If, in addition, the sinus nerves and vagi are cut (303), the response to CO_2 is abolished (302). Ablation of the pneumotaxic center (NPBM) in the rostral pons has been shown by St. John (319) to decrease respiratory frequency and elevate $PaCO_2$, whereas the response to hypoxemia was intact. How these NPBM fibers interact with processing CO_2 signals remains unclear.

Perception of physiological degrees of hypoxemia is classically outside the CNS in the carotid or aortic bodies, where, in addition, acidosis and some chemicals can also give afferent impulses that must be integrated with other determinants of respiration within the CNS. Schlafke (302) has suggested that these peripheral chemoreceptor inputs are: 1) perceived exclusively in the integration area of CO_2 (S); or 2) the CO_2 integration area acts only to amplify (but not inhibit) peripheral signals dependent on O_2. Interestingly, animals with coagulated integration areas (E, fig. 1) display marked respiratory stimulation to peripheral stimuli (e.g. noise), which normally do not effect respiration. Cherniack et al. have recently proposed that area S does not modulate afferent carotid sinus impulses nor hypoxia induced stimulation of respiration (68). In any case, since the integration area may modulate entry of other CNS reticular inputs to respiratory control, drug effects could also be exerted at this region. When the peripheral hypoxia-sensing apparatus is not functional, or if hypoxia is severe, a depression of ventilation occurs by an effect at an unknown site within the CNS (361).

This cursory summation suggests a multitude of points within the CNS at which drugs could alter respiratory activity (see fig. 1 for summary). Since minute ventilation is sensitive to changes in CO_2 in normal animals, any drug that alters the rate of production or removal of CO_2 would alter ventilation. Moreover, if a drug stimulates minute ventilation by a mechanism unrelated to changes in metabolism and CO_2 production, mechanical changes would occur and $PaCO_2$ would subsequently decrease. It is obvious that drug-induced changes in ventilatory mechanisms (frequency, tidal volume, tidal volume/inspiratory time, etc.) can be interpreted best in the light of prevailing arterial CO_2 tensions (231). Since oxygen is not normally of major importance in ventilatory control, and represents events peripheral to the CNS, most investigators pursue experiments under hyperoxic conditions or in animals with denervated carotid bodies to assure the lack of their involvement in experimental results.

Figure 1 also suggests experimental approaches to ask more specific questions as to where and how a particular drug exerts its effects on respiration. First of all, in measuring respiratory activity, integrated phrenic activity is a more reliable index than mechanical parameters such as frequency and tidal volume or their product, minute volume, since effects of drugs on nerve muscle transmission (A, fig. 1) can be avoided. In any case it is critical to know the $PaCO_2$ when measurements of respiratory activity are performed. As to site of drug action, vagotomized and glossopharyngectomized animals can be used to assess the importance of lung mechanoreceptors or peripheral chemoreceptors in drug responses (F, G, fig. 1). High mesencephalic brain stem transections can assess drug actions on forebrain structure (K, fig. 1), and transection at the medulla-pons junctional area can remove drug effects located in the pneumotaxic area (I, fig. 1). The input and participation of spinal cord (C, fig. 1) or other sensory afferents (e.g. trigeminal nerve) in drug responses can be approached by low cervical cord transections (for C, fig. 1), or gasserian ganglionectomy, etc. Direct interventions to remove or stimulate the dorsal or ventral respiratory groups are the most difficult to achieve, although promising experiments with kainic acid (21), iontrophoretic application of drugs (64), and selective stimulation (318) have now begun and hold promise for the future.

It is also conceivable that drugs may produce dramatic changes in respiratory frequency or tidal volume, but because of opposite changes in some other control parameter, no net change in alveolar ventilation (and thus $PaCO_2$) occurs. Studies of these drugs are not irrelevant to our understanding the neuropharmacology of respiratory control, since they may give insight into the neuro-

mediators involved in respiratory timing rather than respiratory drive.

Several neurotransmitters and neuromodulators will be discussed in this review. Since biogenic amines have been demonstrated to interact with respiratory function, figures 2, 3, and 4 indicate the locations of biogenic amine neurons in relation to respiratory cell groups. For earlier reviews on topics covered here and a consideration of additional topics, e.g., acetylcholine, histamine, prostaglandins, etc., the reader is referred to the works of Eldridge and Millhorn (103) and Widdicombe (358). These figures will be referred to when the locus of other neurotransmitter systems in relation to respiratory neurons needs description.

III. Serontin

A. Location

Serotonin-containing cells in the braim stem are located in the raphe nuclei of the midbrain, pons, and medulla (26, 84) (see figs. 2–4). Palkovits has measured the serotonin in single brain stem nuclei of the rat by using the punch technique and found that there are appreciable amounts of serotonin (9–11 ng/mg of protein) in the parabrachial nuclei and nearby locus coeruleus in the pons, with values of the NTS and nucleus ambiguus slightly lower (6–10 ng/mg of protein) (268). There was little difference between the various nuclei in the reticular formation whether tied to respiratory function or not. Histological fluorescence studies in the cat reveal a distribution of serotonin-containing neurons similar to that of the rat. Thus, it would appear that nuclei whose neurons fire in phase with respiratory activity receive an appreciable number of serotonin-containing nerve terminals. Besides being located in close proximity to respiratory relevant areas, the functional activity of serotonergic neurons is altered by hypoxia and hypercarbia. Carlsson et al. (61) observed that hypercarbia induces an increase in brain tissue oxygen tension that occurs with CO_2-provoked cerebrovascular vasodilation. Carlsson's group (61, 132) has more recently observed that the utilization of serotonin is also increased during CO_2 exposure. Although the simplest explanation of these results is that tissue oxygen tension directly alters serotonin synthesis, these responses could be due to less direct changes in neural activation.

B. Respiration Effects

Florez et al. (121) first reported that *p*-chlorophenylalanine-induced inhibition of 5-hydroxytryptamine (5-HT) synthesis increased respiratory frequency, minute volume, and response to CO_2 in decerebrate cats, whereas α-methyltyrosine depressed respiratory activity. These studies suggested a modulatory role for CNS monoaminergic activity in respiratory control. Armijo and Florez (7) subsequently found that in decerebrate or intact anesthetized cats, L-tryptophan and 5-hydroxytryptophan depressed respiratory frequency and minute volume, which produced apneustic breathing under basal and high CO_2 states. These responses were potentiated by monoamine oxidase inhibitors but were prevented with intracerebral administration of a L-aromatic aminoacid decarboxylase inhibitor (7). In cats, tranylcypromine alone markedly stimulated respiration. Moreover, since midcollicular transection did not affect the response to serotonin, the effects probably are exerted in the brain stem. We have now confirmed these effects of R0-4-4602 in halothane-anesthetized rats (208), and have observed that intraventricular 5-methoxy-N,N-dimethyltryptamine, a serotonin agonist, depressed respiration and that this response is potentiated in animals whose serotonergic neurons were partially destroyed at 3 days of age with intracisternal administration of 5,7-dihydroxytryptamine to selectively destroy serotonergic nerve terminals (202). The depressant effect of serotonergic agonists on respiration is observed whether the 9th and 10th cranial nerves are intact or divided, again suggesting a central mechanism of action (208).

One of the more curious expressions of serotonin precursor or agonist administration in the rat is that as the tidal volume progressively declines, the CO_2 response is obtunded, and the inspiratory pressure tracing resembles the apneustic pattern seen in animals treated by denervation of the vagus and ablation of the pneumotaxic center (208). Moreover, this response characteristic is unchanged by vagotomy. Perhaps increased serotonergic receptor stimulation inhibits expression of NPBM and vagal afferent impulses to the respiratory neuronal groups to terminate inspiration. Alternatively, perhaps in the course of terminating inspiration, the pneumotaxic center or vagal afferent impulses traverse a serotonergic neuronal group more proximate to the ultimate respiratory generator. A test of sensitivity to serotonin agonists in animals with ablation of the pneumotaxic center and with intact or deficient CNS serotonergic innervation should resolve this question. Since direct application of serotonin to dorsal respiratory neurons produces responses that are inconsistent, but usually depressant, the interaction is probably at some neuronal subpopulation of these neurons or at a site prior to impulse arrival at the dorsal respiratory group (114), which in part represent upper motor neurons for phrenic motor neurons. Curiously, a few of the serotonergic neurons of the B5 group are located as far lateral as the region of the NBPM (277) (see fig. 3). The suggestive evidence obtained in intact cats and rats by using mechanical indexes of respiration (see above) have now been confirmed with phrenic neurograms (222).

Lambert et al. (199) found that in urethane-anesthetized rats, respiratory rate and depth was decreased by 1 to 25 μg of serotonin given into the cerebral ventricles. Thus, the response seen in animals anesthetized with this excitatory anesthetic resembles that reported in halothane-anesthetized rats. Moreover, Olson et al. (262) have observed that both *p*-chlorophenylalanine- and *p*-

chloroamphetamine-induced serotonin depletion decreased $PaCO_2$ by 5 to 9 torr in awake rats; thus the serotonin effects would not seem to be secondary to some interaction with the anesthetic used. The lack of an unequivocal effect of 5,7-dihydroxytryptamine-induced serotonin depletion on respiration in their studies on awake rats may be due to inadequate serotonin depletion in their rats, or the compensation produced by supersensitivity to serotinin that develops after administration of this neurotoxin to adults (208, 262). Mitchell et al. have recently reported that *p*-chlorophenylalanine increases respiration in awake goats and that the carotid bodies were not involved in this response (234). Moreover, the respiratory responses to hypercapnia and exercise were not altered by this pharmacological impairment of serotonin function.

The ability of the serotonin receptor antagonist methysergide to reverse the inhibition of respiration produced by serotonergic receptor agonists sheds some light on the neurochemical and neurophysiological mechanism of the response (208, 241). Serotonin iontophoretically applied to CNS neurons can produce either an excitation or inhibition. However, only the excitatory responses are inhibited by methysergide (3). Based on intracellular recordings of rat facial motor neurons, serotonin application facilitates both synaptically mediated and glutamate-induced excitation, perhaps by changing potassium conductance (334). This response could be blocked by application of methysergide. Since the depressant effects of serotonin on respiration are easily reversed with serotonin antagonists, it would follow that a serotonin-mediated excitatory response would somehow decrease minute ventilation. Thus, the serotonin interaction with respiratory drive would resemble that of afferent vagal stretch or J receptor impulses, whose effect is to decrease minute ventilation. Serotonin neuron-mediated inhibition of monosynaptic spinal cord reflexes, which is antagonized by serotonin antagonists, resembles the above respiratory interactions of the transmitter (71, 283).

All serotonergic agonists may interact with serotonergic transmission in at least two ways: 1) by combining with postsynaptic neurons normally innervated by serotonergic neurons; or 2) by combining with presynaptic neurons themselves, thus decreasing serotonergic firing rate and amine release. Of the various serotonergic agonists that depress respiration, the ratio of pre-synaptic to postsynaptic efficacy after iontophoretic application varies from 4.3 for 5-methoxy-N,N-dimethyltryptamine to 0.17 for serotonin itself, largely as a result of dissimilar efficacy at postsynaptic receptors (91). Since serotonin only depresses raphe neurons, and the depressant effects of 5-methoxy-N,N-dimethyltryptamine are unaltered by depletion of serotonin with reserpine (198), the respiratory effect described after administration of serotonin agonists are probably not due to autoreceptor stimulation, but due to activation of postsynaptic receptors at some other site. Fallert et al. (114), by using microelectrophoresis of serotonin on respiratory related medullary cells of urethane-anesthetized rabbits, found that excitation was the usual response of neurons that fired in both inspiration and expiration, whereas half of the cells firing in inspiration only responded with inhibition more often than with excitation. Thus, a subpopulation of either cell type could furnish the basis of respiratory effects of serotonergic perturbation. No differences in response to transmitters were observed in Rα or Rβ dorsal respiratory group cells, so we cannot yet localize the functional neuronal pool directly involved in the response to serotonin.

Not all respiratory responses to serotonin agonist administration to the CNS are inhibitory. Some investigators have occasionally reported stimulation of respiratory activity after administration of serotonin agonists. Armijo et al. (8) have observed that in lightly anesthetized cats, application of serotonin (50–500 μg) to the lateral ventricle initially induced a brief increase in frequency and tidal volume, followed by a subsequent more pronounced depression of these parameters. Only depression was observed if the compound was given in the fourth ventricle, and brain transection experiments suggested that the stimulating effect observed after lateral ventricle injection is probably suprapontine in location. Millhorn et al. (233) have also observed a poststimulus increase in the phrenic neurogram index of respiratory activity when serotonin was placed in the ventricle system of the cat, and this could be blocked by methysergide. They concluded that the increased respiratory activity could be due to serotonin-mediated pathway that enhanced respiratory activity. It is thus conceivable that depending upon the region of brain where the serotonergic agonist effect is more profound, an increase or decrease in respiration can be produced.

It is interesting that in some groups of awake or halothane-anesthetized rats pretreated at 3 days of age with 5,7-dihydroxytryptamine to selectively deplete serotonin, the response to CO_2 is blunted and resting CO_2 values are elevated. At first glance, this would seem to argue against the physiological involvement of serotonin-containing neurons in tonically depressing respiratory activity. However, respiratory depression produced by parenteral (208) or intracerebroventricular (i.c.v.) (241) serotonergic agonist administration is markedly potentiated in 5,7-dihydroxytryptamine-treated rats. The development of supersensitivity of serotonin receptors involved in other endocrine and behavioral responses is well known in rats given this serotonergic neuronal toxin (48). It would, however, seem unusual to have such marked supersensitivity develop that the responses to serotonin release from remaining nerve terminals would be greater than normal, i.e. produce respiratory depression.

Another explanation for the decreased respiration in 5,7-dihydroxytryptamine-treated rats is also possible. Serotonergic neurons have recently been found to contain

other possible neuromodulators. For example, the rat ventral medulla oblongata contains several nuclei in the reticular formation that contain both serotonin and substance P (nucleus raphe pallidus, raphe obscurus, gigantocellularis, paragigantocellularis lateralis, and interfascicularis hypoglossi) (66). Thyrotropin-releasing hormone (TRH) has also been observed in serotonergic cell groupings (165), and we have found that brain stem TRH-like immunoreactivity is transiently decreased by 5,7-dihydroxytryptamine (45, 46). Thus, TRH or substance P, both of which are respiratory stimulants (see peptides, below), may be deficient in these animals, thus producing a deficient basal respiratory drive. In fact, rats with reduced serotonin are supersensitive to the stimulating effect of i.c.v. TRH (240).

It also seems possible that CNS serotonin mechanisms may be involved in the respiratory responses to hypoxia and hypercarbia. Since Carlsson's group has found that high CO_2 exposure elevated serotonin synthesis and release in the brain stem (132), it seems possible that serotonin neuronal systems might function to counteract changes in minute ventilation induced by CO_2 inhalation, thus serving a modulatory function on respiratory activity. In support of this theory, inhibition of serotonin receptors with methysergide or depletion of serotonin with *p*-chlorophenylalanine augments the minute ventilation-CO_2 response curve (208, 241).

Zaleska (370) has observed that brain stem serotonin is increased in rats given 7% oxygen to breathe and is accompanied by a sharp decrease in 5-hydroxyindoleacetic acid (5-HIAA), which suggests decreased serotonin utilization during pentobarbital anesthesia. In animals without peripheral chemoreceptor function, hypoxia produces profound respiratory depression. Perhaps one of the compensations that attempts to override this central hypoxia-induced hypoventilation is a turn-off of inhibitory serotonin inputs.

The above speculation emphasizes that rather than focusing only on how serotonin-containing neurons affect respiration, we should also consider how respiratory changes and reflexes might alter serotonergic neuron function. Afferent impulses from the lungs, via the vagal nerves, may reflexly alter central serotonergic neuron function. Sole et al. (316) have observed an inhibition of serotonin turnover in nerve terminals in the medulla and hypothalamus in rats after acute coronary artery ligation. Both the CNS transmitter changes and bradycardia could be prevented by topical application of lidocaine to the wall of the left ventricle. It is thus conceivable that normal brain serotonergic neurons participate in modulating reflexes initiated by changes in afferent vagal activity (202). In addition, sinoaortic denervation of rats decreased resting midbrain serotonin for 1 week, whereas the pons-medulla content increased markedly for the first 24 hours. These changes are accompanied by an increase in 5-HIAA, which suggests that the utilization of serotonin is increased (67).

C. Physiological-Pathological Interactions

Respiration is altered by many normal physiological processes such as sleep and pain perception. These two phenomena are accompanied by dramatic changes in serotonergic function. Orem (264) has recently demonstrated that during phasic rapid eye movement (REM) sleep in cats the discharge of inspiratory and expiratory cells increased in number and frequency. Ventral medullary respiratory activity generally was decreased during tonic REM, whereas dorsal group cells were variously activated or inactivated. It is curious that the increased respiratory neuron activity during REM sleep occurs under conditions in which serotonergic neurons are relatively quiescent (3). It is conceivable that the disorganized respiratory pattern that develops during REM sleep is a consequence of the loss of serotonergic inhibition. In fact, Baker and McGinty (14) reported that hypoxia-depressed respiration in kittens when awake or in non-REM sleep is reversed in REM sleep. Recently, elevated 5-HIAA concentrations in cerebrospinal fluid (CSF) in patients with sleep apnea syndrome have been reported (18, 78, 215). Although 5-HIAA in CSF is not a simple estimate of serotonin release in brain (53), an elevation in 5-HIAA would be compatible with increased serotonergic neuron activity in these individuals. Therapeutic attempts might be made with drugs or dietary regimens that would decrease serotonin availability or receptor activation.

The importance of pain, especially during surgery, in altering respiratory activity is well known. It is of interest that several lines of evidence have implicated serotonin-containing neurons in nociceptive responses [see Messing and Lytle (228) for review]. One widely held interpretation of this area is that increased serotonergic neuronal activity is associated with less perception or reactivity to pain, and decreased nerve activity enhances pain response. Moreover, stimulation of a peripheral nerve at 1 Hz in chloralhydrate-anesthetized rats decreases serotonergic neuronal depolarization rate (4). Thus, inhibition of a tonic serotonergic modulation of respiration could be responsible for the increase in respiratory activity seen with a painful stimulus. Although it is tempting to propose that the respiratory depression induced by increased serotonergic activity involves an endorphinergic link, pretreatment with a high dose of naloxone (40 mg/kg i.p.) in halothane-anesthetized rats does not significantly interfere with the ventilatory depressant effect of 5-methoxy-N,N-dimethyltryptamine (10 mg/kg i.p.) (Mueller et al., unpublished observations).

IV. Dopamine

Animal studies have revealed a depressant effect of dopamine on peripheral chemoreceptor activity (298), and in man, infusions of dopamine depress both basal and hypoxic but not hyperoxic ventilation states (354). In the dog, however, dopamine facilitates the chemore-

ceptor discharge (27), and intravenous infusion of dopamine to halothane-anesthetized cats stimulates respiration by a mechanism that can be blocked by section of both the vagal and glossopharyngeal nerves (209). Besides this peripheral effect of dopamine on respiration, there also seems to be an effect of this neurotransmitter on respiration within the CNS.

A. Location

Several authors have described dopamine-containing neurons in the caudal brain stem (335, 238) with the demonstration of appreciable amounts of dopamine in nerve terminals in the areas relevant to respiratory control. One of the most detailed efforts to map catecholamine-containing neurons in the cat unfortunately used a technique that does not allow one to differentiate norepinephrine from epinephrine or dopamine-containing fibers (197). In the cat, caudal brain stem catecholamine-containing fibers were found: 1) in the ventrolateral medulla oblongata in and near the lateral reticular nucleus, from the inferior olive caudally to the spinal cord; 2) in the commissural, medial, and lateral nuclei of the solitary tract; 3) cranial to 1 above, adjacent to the facial nucleus and the superior olive; and 4) in the dorsolateral pons [nucleus locus coeruleus (1C), subcoeruleus, Köelliker-Fuse nucleus, and the medial and lateral parabrachial nuclei]. Again, as with serotonin, these amines are distributed to areas intimately related to respiratory control.

B. Respiratory Effects

Results in intact, halothane-anesthetized rats have demonstrated an increase in respiratory rate upon i.p. or i.v. administration of apomorphine, a dopamine receptor agonist (205, 207). This tachypnea is accompanied by a decrease in tidal volume with no significant change in $PaCO_2$ observed at doses that produce profound behavioral changes in awake rats. Apomorphine also increased the mechanical responses to CO_2 exposure (205). Haloperidol antagonized these changes at doses that did not produce any change in respiratory parameters in rats not given apomorphine. Although vagotomy abolished the tachypneic response to apomorphine, tidal volume was then increased, so minute ventilation remained elevated over control values (207). Glossopharyngectomy did not alter the response to apomorphine. However, the effect was potentiated in animals whose CNS dopamine-containing neurons were destroyed at birth with 6-hydroxydopamine (207). In animals that received neonatal 6-hydroxydopamine treatment to destroy dopamine-containing nerve terminals, the basal minute volume was less than in controls, whereas the response to CO_2 exposure showed less relative change in rate but a greater relative increase in tidal volume. This would suggest that in normal rats dopamine-containing neurons participate in respiratory control, albeit probably indirectly, and probably affect primarily respiratory timing rather than respiratory drive.

Not all studies of CNS dopamine agonists on respiration have concluded that a stimulation is produced. In chloralose-anesthetized rats, Bolme et al. (35) noted that the respiratory rate and blood pressure were significantly reduced after i.v. apomorphine and pimozide, a dopamine antagonist, blocked this decrease. Unfortunately, the resting respiratory frequency of these animals was not provided. If frequency was depressed, it may provide an explanation for the lack of stimulation observed after apomorphine. In the above study intracisternal administration of very high doses of apomorphine (100 μg) produced only a modest (10%, although significant) decrease in respiratory rate, and lateral ventricle administration of 30 μg was without effect on respiratory rate. Opposite changes in tidal volume were measured. Although no blood gas data were provided by which to judge the biological relevance of this modest change in respiratory timing induced by apomorphine, $PaCO_2$ was probably unaltered. Since the i.v. dose that affected respiration was larger than that necessary intracisternally, the drug presumably exerted its effect within the CNS. Farber and Maltby (116) studied Dial-urethane-anesthetized rats with the cervical vagal and sympathetic trunks sectioned. In this model s.c. administered apomorphine resulted in a haloperidol reversible reduction of respiratory frequency and minute ventilation. In this preparation, however, an influence of peripheral chemoreceptor activity could be involved, as glossopharyngectomy was not performed.

It is possible that the type of anesthetic agent could contribute to the difference in response observed with dopaminergic agonists. Nieoullan and Dusticier (257) have examined the effects of α-choralose and halothane anesthesia on the release of ^{3}H-dopamine from the caudate nucleus and the substantia nigra, by using a push-pull cannula technique after ^{3}H-tyrosine loading. The release rate of ^{3}H-dopamine was lower and took a longer time to achieve steady state under chloralose anesthesia than with halothane anesthesia (the highest) or after encephalé isole preparations (intermediate). Unilateral somatic stimulation of chloralose-anesthetized animals did not alter the basal dopamine release, whereas in halothane-anesthetized preparations the release rate was altered and may even have been increased as a result of greater dopaminergic neuron stimulation (255). This anesthetic-dependent change in response was speculated to reflect greater γ-aminobutyric acid (GABA) inhibition of dopamine neuron activity under α-chloralose anesthesia (257, 293). It should be pointed out, however, that Massotti and Longo (219) have not observed an effect of α-chloralose on dopaminergic neurons of rat brain.

A recent preliminary study compared the respiratory effects of a rather high dose of i.c.v. apomorphine (300 μg) in rats lightly anesthetized—to the point of accepting the endotracheal tube—with urethane, chloralose, chloral hydrate, halothane, or enflurane. All anesthetics, except halothane and urethane, decreased basal respiratory rate per se. The increase in respiratory frequency

after apomorphine was greatest in halothane-anesthetized, and somewhat less in urethane-anesthetized rats, but no stimulation was observed in animals subjected to chloralose, chloral hydrate, or enflurane anesthesia. Thus, the effect of the dopamine agonists seems to vary with the basal state of CNS excitation (149).

Examination of the behavioral effects of dopamine agonists has revealed that the observed responses are highly dose dependent. Thus, studies of apomorphine on locomotor activity show that low doses produce sedation, whereas high doses induce hypermotility and sterotypy (321). Carlsson (58) has presented data which suggest that low doses of apomorphine or other dopamine agonists that decrease locomotor activity and the spontaneous release of dopamine do so by stimulating presynaptic autoreceptors. The activation that follows larger doses of these agonists is postulated to be due to direct postsynaptic receptor activation. Presumably the response seen with apomorphine would depend on existing basal availability of endogenously released dopamine, which in turn is proportional to the rate of depolarization of dopaminergic neurons. If, as discussed above, this rate is high in halothane-anesthetized rats the increased respiratory frequency observed may be due to predominantly postsynaptic receptor activation. Conversely, in chloralose-anesthetized rats with very little spontaneous release, the same dose of dopamine agonist might be sufficient to stimulate only presynaptic receptors and thus inhibit further dopamine release and diminish postsynaptic receptor activation and depress respiration. Thus, postsynaptic dopamine receptor activation in both cases would increase respiratory frequency. Padron (265, 266) observed a stimulatory effect of two dopamine receptor agonists: amantadine (high doses) and with some doses of bromocriptine. With the latter drug an initial short duration depression in respiratory rate was noted, and Florez et al. (personal communication) have recently observed a similar biphasic response after i.c.v. administration of dopamine. Padron and Florez (266) also reported that in intact urethane-anesthetized rats the only change in minute ventilation after bromocriptine was a stimulation and that phentolamine i.c.v. prevented this increase, which suggests that noradrenergic receptor activation was responsible for the respiratory response. Unfortunately, blood gas or end tidal CO_2 data were not provided to judge the physiological consequences of this respiratory stimulation, nor was it determined whether the effects were exerted in the CNS.

Mediavilla et al. (personal communication), who have recently studied the effects of i.c.v. dopamine on respiratory mechanics of thiopental-urethane anesthetized rats, found 30 to 300 μg doses initially decreased the frequency (7%–8%) but this was followed by a later stimulatory phase (14%–19%). Pretreatment with monoamine oxidase inhibitors, chlorgyline or deprenyl, prevented the initial depression and enhanced the later stimulatory phase. Haloperidol (but not phentolamine) inhibited the monoamine oxidase inhibitor enhanced increase in respiratory frequency after dopamine. The biphasic nature of the response could be due to variable penetration of dopamine into various CNS locations or to activation of different dopamine receptors (76, 315).

In halothane anesthetized rats, Hedner et al. (149) found that 300 μg, but not 30 μg, of i.c.v. apomorphine affected respiration in a biphasic manner. An early and short-lasting (5 min) decrease in respiratory rate and increase in tidal volume (phase I) was followed by a sharp increase in frequency and a decrease in tidal volume for about 45 minutes (phase II). Systemic haloperidol (2 mg/kg i.p.) blunted the early response and abolished the late apomorphine effect. Haloperidol administered alone i.c.v. (0.3–30 μg) produced an immediate decrease in respiratory rate and a slightly increased tidal volume, a response that resembled the phase I effect of apomorphine. A similar respiratory response was also achieved by i.c.v. injection of 3-(-3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP), a presumed presynaptic dopaminergic agonist (160). The results would seem compatible with postsynaptic stimulation that increases respiratory rate, but probably relate more to respiratory timing than to regulation of respiratory control.

It has become apparent that release of dopamine may not be similar at all portions of the neuron. For example, unilateral stimulation of the cerebellar dentate nucleus decreases ^{3}H-dopamine release from ipsilateral caudate nucleus (nerve terminal area), but enhances release in the contralateral nucleus (256). Simultaneously, the release of ^{3}H-dopamine from the contralateral nigra (cell body region) was reduced and that of the ipsilateral nigra increased. Somatic touch or special sensory stimuli produce opposite effects. Thus, dendritic release and axon nerve terminal release are probably not only of different magnitude, but may even be of opposite directions (256), and some of the disparity between dopamine agonists administered systemically and by i.c.v. may be due to different effective concentrations achieved in relevant brain areas.

By using a plethysmographic measurement of respiratory rate in awake mice, McGilliard and Takemori (223) observed that 1-dopa methyl ester stimulated respiratory rate at doses of 200 mg/kg (but not 100 mg/kg), whereas doses of 0.5 to 2 mg/kg of haloperidol decreased the rate, and pimozide at doses of as much as 2 mg/kg were without effect. With microelectrophoretic administration of flupenthixol, a dopamine antagonist, as a relatively specific test of the importance of dopamine to cell stimulation, Bohmer et al. (31) observed that in urethane-anesthetized rabbits, inspiratory neurons were excited by flupenthixol and expiratory or inspiratory-expiratory neurons were largely inhibited when responsive. The data are hard to integrate with respiratory control, but could imply a net inhibitory effect of dopamine on neurons possibly involved in respiratory timing, and would seem to foster short inspiratory phases, thus increasing respiratory rate. These results fit nicely with earlier reports in which a direct inhibition of inspiratory

cells by dopamine applied electrophoretically was observed (114).

In addition to presynaptic and postsynaptic effects of apomorphine, indirect changes produced by actions of this agonist on serotonergic neurons may also contribute to responses. Grabowska (138) has observed that apomorphine accelerates the disappearance of serotonin after inhibition of its synthesis, and also increased 5-HIAA content at doses that produced stereotypy as an endpoint. Mogilnicka et al. (237) observed that methysergide (5 mg/kg) potentiated the locomotor response to apomorphine, yet Baldessarini did not observe such an interaction (15). Grabowska subsequently observed that the apomorphine-induced increase in mesencephalic 5-HT and 5-HIAA was prevented by an acute transection at the rostral mesencephalon (139). Thus, reflexes through diencephalic structures would seem to be involved in these changes.

A stimulating effect of hypercarbia on tyrosine hydroxylation (in norepinephrine, dopamine, and epinephrine CNS neurons) has been reported even when PvO_2 of cerebral venous blood was kept constant (88, 89, 132). Thus, the augmented catecholamine synthesis in hypercarbic animals, since not related to changes in oxygen availability for tyrosine hydroxylation, must be secondary to some other, indirect effect, possibly secondary to a change in neuronal pH directly or secondary to stimulation of some other (possibly a chemoreceptor) neuronal system that activates central catecholaminergic pathways. Carlsson's most recent findings suggest that not only synthesis rates are altered by CO_2 exposure, but also the utilization of norepinephrine and serotonin is increased and that of dopamine is decreased by hypercarbia in intact spontaneously respiring rats (132). However, the data presented do not permit one to determine whether these changes are related to the altered motor activity induced by hypercarbia, or are a result exclusive of that response. In man, for instance, physical activity can alter homovanillic acid accumulation after probenecid administration (280). In addition, the possible role of these amine changes in facilitating the hyperventilation produced by CO_2, or the converse, inhibiting the hyperventilation by some effect directly on CO_2 perception or CNS respiratory integration systems as discussed above, is also unknown. Carlsson speculates that the pattern of changes in monoamine synthesis is superficially similar to that induced by GABA administration (132), and that changes in this transmitter or modulator system may be a secondary or even the primary link of hypercarbia to monoaminergic activation. The above studies by Carlsson have not quantified the role of any of the biogenic amine responses to the central respiratory responses to CO_2 or O_2.

The effects of hypoxia on brain biogenic amine synthesis and utilization have also been examined by Davis and Carlsson (88) and by Davis et al. (89). However, although the effects of hypercarbia and hypoxia on synthesis of biogenic amines are dissimilar, their effects on transmitter utilization are similar. Thus, hypoxia, like hypercarbia, produces an inhibition of dopaminergic and stimulation of noradrenergic activity (51, 132). All of these studies were done in intact animals, and respiratory mechanical responses to these perturbations were neither measured nor controlled.

C. Physiological-Pathological Interactions

The concept that catecholamines and serotonin have antagonistic actions in the CNS is not new. Based on pharmacological studies Brodie and Shore (50) suggested that ergotropic functions involved norepinephrine and trophotropic or vegetative actions serotonergic neurotransmission. A similar interpretation has been applied to observations of drug effects on locomotor activity, with dopamine often interpreted as acting in concert with norepinephrine neurons to increase activity, and serotonergic activation serving to decrease motor behavior (296). The two types of amine systems can probably interact directly since serotonergic nerve terminals have been observed both in the caudate nucleus (85, 276), as well as the substantia nigra (269). Even drugs such as neuroleptics, widely known for their ability to block dopamine receptors, can antagonize the 5-HTP syndrome at doses 2- to 7-fold less than that needed to produce catalepsy, with the anti-5-HTP syndrome potency being unrelated to cataleptogenic effects (210).

The use of rats for studies of respiration has the potential advantage that the genetic bases for respiratory control may now be approached. Thus, selectively bred, spontaneously hypertensive rats have a greater motility response to amphetamine than do the stock Wistar-Kyoto rats from which they were derived (220). These differences could be abolished by depleting catecholamine stores in brain or inhibiting serotonin synthesis in the control strain. Two strains of mice have been found that possess an unequal number of dopamine-containing neurons (13), which establishes that there is genetic control of the number of specific neurons in mammalian brain. With many strains of rats, including backcrosses already available, a systematic search of such strains for unequal sensitivity to neurotransmitter perturbations of respiration or response to afferent stimuli might suggest profitable avenues for further research.

The ability of exercise to increase respiratory minute volume is well known but still not fully understood. This is one area that may be closely linked to biogenic amines, as evidenced by the known potency of dopamine agonists to increase motor activity and serotonergic systems to blunt these responses (42), a relationship that could be duplicated by observations with these two neuronal systems on respiration. Arterial CO_2 tension does not rise with exercise, and indeed may fall with exercise, and PaO_2 increases; thus a CNS neuronal (cortical, basal ganglia, cerebellar, or brain stem collateral) network may be responsible (24, 348, 350). An intact passively exercised

extremity increased minute ventilation, but cutting the nerves to the extremity abolished this increased respiratory activity (49), as does transection of certain fibers in the spinal cord (221). Repeated strenuous exercise training could exert tonic changes in respiratory control, perhaps as a result of repetitive activation and induction of rate-limiting enzymes that synthesize transmitter (243). In fact, trained athletes evidence diminished responses to both hypercapnia and hypoxia (57). It is thus obvious that the importance of motor activity in CO_2-induced changes in serotonin or dopamine synthesis and release are critical if these transmitters are also involved in respiratory control, since it is known that they are closely related to motor activity.

Eldridge et al. (104) have recently observed that in decerebrate cats induced to increase locomotor activity on a treadmill by subthalamic stimulation, the increased respiratory activity actually preceded changes in locomotor activity. This relationship held even after removal of most respiratory afferents, and in paralyzed animals the initial respiratory increase persisted. They suggested hypothalamic signals may be responsible for the proportionality of respiratory activity and locomotion during exercise. Since dopaminergic-mediated respiratory changes induced after i.c.v. administration show the same biphasic character as does the locomotor response in cats, it is possible that dopamine-containing neurons may participate in exercise-induced changes in respiration.

Since dopamine turnover is increased in rodents when exposed to foot shock, immobilization stress, or avoidance experiences, the hyperventilation that is a part of the response to fear may be an indirect consequence of increased dopaminergic neuronal activity (28).

Aminophylline is widely used to decrease the severity and incidence of apneic episodes in the newborn (86). The responses of the halothane-anesthetized rat superficially resemble those of the human newborn (206) with an increase in respiratory rate and minute ventilation and increase in the ventilatory response to CO_2. In the rat (206) and the cat (105) the stimulatory effect could be blunted or abolished by haloperidol or α-methyltyrosine (105). Subsequent studies revealed that acute section of the vagus and glossopharyngeal nerves did not alter the aminophylline-induced stimulation (206), but neonatal destruction of CNS dopamine-containing neurons with desmethylimipramine and 6-hydroxydopamine abolished it (242). Animals with deficient CNS serotonin-containing neurons after neonatal pargyline plus 5,7-dihydroxytryptamine displayed an increased sensitivity to aminophylline, and the depressant effect of 5-methoxy-N,N-dimethyltryptamine in intact rats was enhanced (242). These data demonstrate that the respiratory response to aminophylline is the summation of the effects of this drug on CNS dopamine and serotonin neuronal systems. Indirectly, these data imply that CNS monoaminergic neurons may play a role in the pathogenesis of neontal apnea syndromes.

Recently, two studies have suggested that the respiratory stimulation observed after aminophylline may be in part due to antagonism of the respiratory depressant effects of adenosine, since aminophylline antagonizes the depressant effects of adenosine analogues, 2-chloroadenosine (244) and 6-N(L-phenylisopropyl) adenosine (106).

Bainbridge and Heistad (12) infused dopamine in normal men whose ventilation was stimulated by breathing hypoxic gas mixtures, and noted that dopamine inhibited this ventilatory response. Haloperidol, 2.5 mg i.m. (12), could reverse the dopamine effect, but haloperidol alone did not alter minute ventilation or $PaCO_2$ during normoxia or hypoxia. They concluded that endogenously released dopamine does not significantly alter chemoreceptor afferent impulse flow under normal conditions. It is also possible, however, that the haloperidol doses sufficient to block exogenous dopamine infusions do not block endogenously released amine. Alternatively, the lack of response to haloperidol in man in the absence of dopamine may be due to the antagonistic nature of the central and peripheral dopamine receptors in man. The blunting of hypoxic drive by dopamine, often infused into critically ill patients, may be a significant hazard in those patients with a depressed central respiratory response to CO_2 (190). The authors are unaware of the respiratory effects in man of dopamine agonists, such as apomorphine and bromocriptine, that penetrate the CNS.

Patients who receive neuroleptic drugs chronically are subject to tardive dyskinesia, a specific drug-induced movement disorder, which appears to affect mechanical indexes of respiration as well (177). In eight patients with this condition a faster respiratory rate and more variable rate was evidenced compared to matched controls on neuroleptics without tardive dyskinesia symptoms. These findings agree with anecdotal reports of respiratory distress and hyperventilation in this subset of patients who received long-term administration of neuroleptic drugs (62, 359).

V. Norepinephrine and Epinephrine

It has been almost three decades since Whelan and Young (357) first noted that peripheral administration of epinephrine stimulates respiration. The receptors responsible for this response and their location in the CNS or in the periphery have been studied, but with conflicting results. In man, carotid or vertebral artery infusion of norepinephrine and epinephrine do not alter respiration (74). On the other hand, Schoene et al. recently reported that in awake fasting men the ventilatory response to hypoxia was positively correlated with the magnitude of increase in plasma norepinephrine and epinephrine, and the ventilatory response to hypercarbia was positively correlated with the increase in epinephrine (307). It is not yet clear whether these changes in plasma amines are only one component of the response to respiratory gas changes or contribute to the observed re-

sponse. Regardless of the presence or absence of respiratory responses to peripheral catecholamine administration, it is now apparent that neurons within the CNS that contain either norepinephrine or epinephrine could have effects on respiratory activity.

A. Location

Norepinephrine perikarya in the rat are located in three main groups: 1) the locus coeruleus; 2) the subcoeruleus; and 3) the dorsal motor nucleus of the vagus (324). The pontine locus coeruleus (LC) gives off neuronal projections that contain norepinephrine; these innervate the entire CNS to some degree, but the nucleus itself is located close to, or may comprise a part of the pneumotaxic center (84, 19). By using axonal transport and immunocytochemistry with antibodies to dopamine β-hydroxylase in the monkey, Westlund and Coulter (356) have found that norepinephrine terminals arising from the LC terminate in the dorsal motor nucleus, nucleus ambiguus, and the NTS. Moreover, it appears as though all brain stem nuclei receive noradrenergic terminals from the LC, the locus subcoeruleus-medial parabrachial nuclei, or both.

By using antisera to phenylethanolamine N-methyl transferase to classify neurons as epinephrine-containing, two groups of cells were first observed, designated C_1 and C_2 (163, 164). Howe et al. (174) have recently also described a third group of positive cells (C_3), which are located among the medial longitudinal fasciculus of the medulla, in addition to C_2 in the nucleus of the NTS and C_1 in the ventrolateral area (174). These fibers were found to innervate the dorsal motor nucleus of the vagus, the lateral column of the spinal cord, the LC, and the hypothalamus. Thus, once again juxtaposition of monoamine neurons to several areas associated with neurons that fire in relation to the respiratory cycle is documented.

Takigawa and Mogenson (326) have reported that electrical vagal afferent stimuli inhibited the LC neurons of anesthetized rats. Activation of this nucleus in primates is often associated with restlessness and an anxiety reaction (286). Although blood volume receptors subserving cardiovascular reflexes may account for some of these responses (323), pulmonary vagal afferent fibers could also be involved, thus completing the framework for a role of these neurons in the regulation of respiration. Aston-Jones and Bloom (9) with single and multiple extracellular recordings of LC neurons, have correlated changes in firing rates with spontaneous behavior in unanesthetized rats. Their results led them to propose that the LC participates in phasic processes related to arousal, and that LC neuronal discharge may facilitate activity in neuronal groups involved with processing external stimuli, but suppress those groups engaged in tonic vegetative function. Since any response to the environment necessitates voluntary and reflex changes in respiratory activity, it would not be surprising to observe changes in respiration related to catecholamine perturbations.

B. Respiratory Effects

Not many studies have examined the effect of intracerebral administration of either norepinephrine or epinephrine on respiratory activity, probably because of the mixed nature of receptors that these amines affect. Florez et al. (121) have previously suggested that the respiratory center is stimulated by adrenergic and inhibited by serotonergic tone, although their initial results were somewhat difficult to interpret because the evaluation of these amines was pursued during the assessment of the respiratory depressant effects of morphine. These early workers did notice a reduced tidal volume and CO_2 response in reserpine-treated cats, but again serotonin, dopamine, norepinephrine, and epinephrine systems are all perturbed by reserpine, as well as by monoamine oxidase inhibitors. Moreover, their use of 6-hydroxydopamine (6-OHDA) to evaluate the basis of narcotic-induced respiratory depression is inconclusive even on that point since no data were provided on the specificity or completeness of neuronal ablation. This is a critical question since they administered 6-OHDA in the lateral ventricles of the cat, whereas the intracisternal route in rats produces a more satisfactory depletion of the brain stem catecholamines than can be produced by i.c.v. administration (47). Howard et al. (173) have reported that intraventricular injection of 6-OHDA in cats was much less effective than in rats.

Padron and Florez (266) used rats anesthetized with pentobarbital-urethane to study the interaction of i.c.v. phentolamine upon respiratory changes induced by bromocriptine (see above). A later-developing increase in respiratory rate induced by bromocriptine was antagonized by prior phentolamine treatment; however, the increase in tidal volume was not altered. Thus, to the extent that phentolamine specifically blocks α-norepinephrine receptors in brain, a portion of the respiratory stimulation after bromocriptine may be due to α-noradrenergic receptor stimulation. This matter is clearly unresolved.

In both decerebrate and pentobarbital-urethane anesthetized rats, Mediavilla et al. (224) have observed that the amphetamine-induced increase in respiratory frequency could be blocked by 100 μg of phentolamine i.c.v. but not by propranolol. This stimulation was accompanied by a decrease of one third in end-tidal CO_2. Since decerebrate animals were more sensitive to stimulation by amphetamine, the effects must be exerted in the midbrain or caudally.

Niechaj (252, 253) has demonstrated in frogs that the CNS system of epinephrine-containing neurons and receptors may be important in integrating cyclic respiratory activity. Chlorpromazine and reserpine abolished

the slow cyclic pattern of amphibian respiration, which is supplanted by a purely rhythmic pattern (252, 253). This worker has also observed similarities of this slow cyclic respiratory activity and comparable drug effects on mammalian respiration (254.).

Farber et al. (115) have examined the effects of injection of norepinephrine into the rostral hypothalamus of haloperidol-pretreated rats, and noted an increase in respiratory rate. Since infusion of lidocaine produced similar changes, they interpreted their results to imply that norepinephrine was increasing respiratory frequency by depressing certain structures in the rostral hypothalamus.

Apnea induced in neonatal pigs under 1 month of age by stimulating the superior laryngeal nerve is prolonged in animals given reserpine several days before use (201). The complicated amine perturbations produced by reserpine have already been alluded to, and preclude a simple interpretation, but it is possible that the loss of norepinephrine transmitter contributes to the prolonged apnea. Several studies have found evidence that α-receptor blockade can depress ventilation or the response to CO_2 (301, 349). Folgering (123) has presented convincing evidence that the response to β-receptor agonists in decerebrated, vagotomized, vertebral artery perfused cats is not due to their local anesthetic effects.

Thus, the majority of observations with different techniques in various species suggests that α-agonists may in fact stimulate respiration. However, not all investigators agree on this point. Bolme et al. (32) observed in chloralose-anesthetized rats that although i.p. piperoxane and yohimibine did not alter respiratory depth or rate, these antagonists prevented a clonidine-induced decrease (15%–20%) in respiratory rate and increase in tidal volume. Apparently there was no effect of clonidine alone on minute ventilation, and blood gases were not measured. The blockade by yohimibine and piperoxane was thought to be due to a blockade of epinephrine receptors in brain (33), but the validity of this preferential block remains open, since turnover of norepinephrine was increased. Earlier, Bolme et al. by using halothane-anesthetized, intact, hyperoxic rats, noted a 15% to 20% decrease in respiratory rate 5 to 10 minutes after administration of 10 μg/kg of clonidine i.v. (33). Moreover, after bilateral (but unverified) lesion of the LC, apneustic breathing was produced, much as was seen after administration of serotonin receptor agonists. Unfortunately, blood gases were not measured nor was tidal volume. Finally, Weinberger et al. (352) observed in awake goats that doses of phentolamine and propranolol which markedly blunted cardiovascular responses to α- and β-agonists did not significantly alter the minute ventilation-CO_2 response curve.

Elam et al. (100) examined the effect of CO_2 inhalation on firing rate of single norepinephrine-containing cell bodies in the LC. Elevation of arterial CO_2 over a range of values from 35 to 95 mm Hg caused an immediate, dose-dependent increase in LC firing rate (100) and peripheral sympathetic nerve firing rate (101). These changes were the result of central CO_2 stimulation.

The increase in norepinephrine turnover reported by others upon exposure of rats to hypercarbic environments is probably the biochemical reflection of the increased firing rate. They suggested that since yohimbine increases norepinephrine release and produces anxiety reactions and clonidine inhibits central norepinephrine neuron activity and produces sedation, an increased activity of LC neurons may be responsible for the anxiety produced in man by CO_2 inhalation. Hypoxia also increased LC activity but decreased peripheral sympathetic nerve activity. Only the LC activation was abolished by peripheral chemoreceptor denervation. An involvement of LC neurons in the respiratory response to hypoxia or CO_2 was not addressed.

Fallert et al. (114), by applying isoproterenol microiontophoretically to respiratory related neurons in rabbits anesthetized with urethane, noted that isoproterenol application to inspiratory cells usually produced excitation. With application of norepinephrine, although again both inhibition and activation were noted, activation was more common than inhibition.

In the same preparation and with similar techniques, Bohmer et al. (31) found that yohimbine inhibited expiratory neurons, whereas neurons which fired during inspiration or during both expiration and inspiration were not affected. Propranolol inhibited about one half of the expiratory neurons, and exerted no effects on neurons firing during both phases of respiration.

Champagnat et al. (63) used iontophoretic or microinjection application of norepinephrine and epinephrine, clonidine, and isoproterenol to study the responses of bulbar respiratory and nonrespiratory related neurons in decerebrate cats with 9th and 10th cranial nerves sectioned. Epinephrine decreased the phrenic nerve discharge rate, and epinephrine depressed respiratory related neurons more than did norepinephrine, perhaps reflecting β-receptor sensitivity. Respiratory neurons were no more sensitive whether dorsal or ventral in location or whether susceptible to vagal afferent stimulation. It thus appears that noradrenergic receptor stimulants could alter respiration rate by an effect either within the cell networks closely involved with respiration or in a multitude of other cells not intimately linked to the respiratory oscillator.

CNS norepinephrine-containing neurons appear to receive several different afferent neurons. Immunohistochemical techniques reveal that the LC appears to receive nerve terminals that contain enkephalin (309). In fact, iontophoretic administration of opiates and opioid peptides to cells of the guinea pig LC in vitro produce a stereospecific, naloxone-reversible, membrane hyperpolarization associated with an increase in membrane con-

ductance (271). Serotonin-containing neurons also appear to influence norepinephrine neuronal activity, since electrolytic lesions of the raphe nuclei of the cat increase turnover of norepinephrine in both cerebellum and cortex (284). In the rat, similar lesions increase the content of norepinephrine metabolites in hippocampus and cerebral cortex (193), and lesioning of rats with 5,6-dihydroxytryptamine to destroy serotonin-containing nerve terminals increases tyrosine hydroxylase and dopamine β-hydroxylase activity in the LC area (185). Moreover, this innervation may be reciprocal. Thus, both biochemical and histochemical data provide the basis for noradrenergic or adrenergic afferent fibers traversing to some raphe nuclei (2, 291). The 5-HT afferents, which in turn innervate the LC, are derived mostly from the raphe dorsalis, raphe centralis, and raphe pontis (202).

Dopamine neuronal activity may also alter noradrenergic neuron function. Several investigators have reported that apomorphine could increase the turnover of norepinephrine in mice (274) and rats (211), in whole brain and in rat limbic or neocortex, or in thalamus and hypothalamus (212). Moreover, these responses were blocked by administration of spiperone, a recognized dopamine receptor antagonist. Thus, the effects seen after dopamine receptor stimulants may be partly the result of norepinephrine fiber activation.

C. Physiological-Pathological Interactions

Whereas some initial reports in intact man suggested that beta blockade might be associated with a decreased ventilation response to CO_2 (247) or exercise (301), others have disputed this (270). Recently, Folgering and Braakhekke (124), by using a crossover, double blind design with three beta blockers given at clinically relevant doses, found no effect on resting or CO_2-stimulated respiratory parameters. [Please see Folgering and Braakhekke (124) for a critical review of relevant controversial data]. It is, of course, conceivable that under certain stress situations where release of norepinephrine or epinephrine may be increased and thus β-receptors stimulated endogenously, beta blockade may then produce altered respiratory activity. β-Receptor antagonists do, of course, block the iatrogenically-induced hyperventilation seen with beta agonist infusion (156, 188). Moreover, apnea was recently observed in a neonate who received an over-dose with timolol maleate, a potent beta blocker (263). It is unclear whether the beneficial effects of β-adrenergic blocking drugs in treating patients with the hyperventilation syndrome are due to specific antagonism of the hyperventilation or are a consequence only of the more generalized CNS depression, which the drugs also produce (181, 322). Thus, it is conceivable that in certain medical situations, β-receptor modulation of respiration or its inhibition could be significant.

Many years ago Schaefer (300) reported that, in general, the large individual variations in the response to CO_2 are correlated with the basic respiratory pattern while breathing room air. The low CO_2 response group evidenced a lower frequency but higher tidal volume and higher alveolar CO_2 while breathing room air. He suggested that the different groups expressed different degrees of "adrenal sympathetic response to CO_2" administration, although these observations were subjective.

In this connection, it is interesting that 80% to 90% of the variability in the tidal volume response to CO_2 in man can be attributed to genetic factors, while frequency response is apparently determined by personality and environmental inputs (6).

Engle and Ritchie (111) observed that while clinically hyperthyroid patients have an exaggerated respiratory response to CO_2, their resting CO_2 values are normal. This increased response seemed largely due to an increase in frequency, with tidal volume being little changed. This augmented response fell with treatment, and the authors proposed that it was due to an increased sympathoadrenal response to stress, initiated by the CO_2 inhalation. Administration of exogenous thyroid hormone to normal subjects was not found to increase CO_2 response by Valtin and Tennery (332). Thus, although still well hidden, there may still be some link between peripheral and central changes in noradrenergic-adrenergic activity and ventilatory responses.

VI. γ-Aminobutyric Acid

A. Localization

The neurotropic actions of γ-aminobutyric acid (GABA) have been studied in various mammalian species for more than 20 years. These studies demonstrated that GABA is present in high concentrations in the central nervous system of various animals (112). Only recently has the localization of GABA-containing neurons been integrated from neurochemical, electrophysiological, and iontophoretic investigations. The distribution of GABA varies within the CNS, with high concentrations in the brain stem nuclei as well as the spinal cord (98, 113). Nuclei relevant to respiratory control such as the parabrachial nuclei, NTS, and LC have average concentrations (about 30 nmol of GABA/mg of protein) (333). Direct visualization of GABA-containing neurons in various parts of the vertebrate CNS has been performed by immunocytochemical techniques with antiserum to glutamic acid decarboxylase [an enzyme responsible for GABA synthesis (299)] as a presynaptic marker. Several investigations have stressed that GABA may be one of the most important inhibitory transmitters in the brain (112). Animal experiments have indicated that GABA mechanisms may be involved in several "autonomic functions" such as thermoregulation, (97) circulation (273), and respiration (148, 151, 159, 216).

B. Respiratory Effects

In early investigations, the effects of GABA on respiration were studied after intravenous administration to various species (107, 325). In the rabbit, a respiratory

depression followed by a stimulation was noted by Takabashi et al. (325) while a stimulatory effect in this species was reported by Elliott and Hobbiger (107). Transient apnea has been described after systemic injection of GABA in the rat under pentobarbital anesthesia (169). This effect was rapid in onset and usually terminated within a couple of seconds after the injection. However, the effect was dose-dependent and still persisted after extirpation of the carotid body (168) which indicated that this effect of peripheral administration of GABA on respiration might be of central origin. A major disadvantage with peripheral administration of GABA is that it penetrates the blood brain barrier in limited amounts (285), and thus effects outside the brain must be considered in explaining the response.

In a study on the thermoregulatory effects of intracisternally administered GABA, Sgaragli and Pavan (308) incidentally noted that various doses of GABA induced a marked respiratory depression sometimes leading to transient apnea. Unfortunately, no further description of the nature of the respiratory depressant effect of GABA was provided. In a recent study from our laboratory (148), GABA administered into the lateral ventricle of the halothane-anesthetized rat induced a rapid and marked decrease in both tidal volume and respiratory frequency. These effects of GABA on both parameters were clearly dose-dependent in the dose range from 0.01 to 1 mg, and irregular breathing patterns were only observed after systemic administration (169). These latter experiments were performed under hyperoxic conditions in order to assure that the hypoxemia following severe respiratory depression would not influence the results. Thirty minutes after GABA administration, no significant alteration in arterial pCO_2 was seen, although arterial blood pH fell slightly. Yamada et al. (364) have recently shown that in chloralose-anesthetized cats, intracisternal administration produced depressant effects on mechanical indexes of respiration similar to the above observations (364).

The "GABA receptor" usually refers to the GABA recognition site on the postsynaptic membrane. When coupled with the transmitter there is an increase in Cl^- permeability that results generally in a hyperpolarization and neuronal inhibition (5). Muscimol is a substance which acts postsynaptically via these mechanisms. This compound is more selective and significantly more potent than GABA itself as a postsynaptic GABA receptor agonist (5). When administered i.c.v. to rats, muscimol caused a dose-related decrease in tidal volume and minute volume. In contrast to GABA, muscimol had little effect on respiratory frequency (148). These effects of muscimol were also seen after systemic administration to preterm neonatal rabbits (169) and chloralose-anesthetized intact cats when given into the fourth but not the third or lateral ventricle (364). The reason for the discrepancy in action of muscimol and GABA on central respiratory control mechanisms is unclear. However, there is some evidence for a multiplicity of GABA receptors (180, 196) and recent work has indicated that muscimol might activate only a limited population of GABA receptors (196).

γ-Hydroxybutyric acid (GHBA), a drug that has been used as a hypnotic (320), is chemically closely related to GABA. GHBA has been found in brain tissue and can be formed from GABA (310), although the distribution of endogenous GHBA in the brain indicates that it may act independently from GABA (60). GHBA has been reported to increase GABA in the brain probably via inhibition of GABA transaminase (310). Also, GHBA causes behavioral and biochemical effects similar to those of GABA (60, 310). In contrast to GABA, when GHBA is administered systemically, it passes readily into the CNS. Increasing doses of GHBA (177.5–750 mg/kg i.p.) to rats caused a dose-dependent decrease in respiratory frequency and minute volume without affecting tidal volume (151). This action could be antagonized by picrotoxin, a postulated GABA antagonist (107). In higher doses, systemically administered GHBA abolished the CO_2 induced respiratory stimulation. Puzzling and opposite effects of GHBA were seen after i.c.v. administration (148). By this route GHBA induced a marked increase in respiratory frequency and decrease in tidal volume. These opposite effects of i.c.v. administered GHBA are difficult to explain but suggest that some of the effects of systemically administered GHBA may be due to centrally active metabolites. In addition, the concentration of active compound at various receptor sites may be quite different after systemic and i.c.v. administration. In any case, electrophysiological and receptor binding experiments suggest that GHBA does not directly activate bicuculline sensitive GABA receptors (112). High doses of naloxone have recently been reported to antagonize the electrical and behavioral changes in dopaminergic function induced by GHBA implying that CNS effects may involve kappa or sigma opiate receptors (311). Interestingly, GHBA has recently been successfully used to manage a case of human narcolepsy with sleep apnea (214). Baclofen (*p*-chlorophenyl-GABA) has been claimed to possess GABA-like properties and is used clinically as a spasmolytic agent (25). Overdosage of baclofen in a young female human has been reported to result in a respiratory failure (134). However, the respiratory effects of baclofen after i.c.v. administration to rats also differ from those of GABA (148). Thus, a marked dose-dependent increase in respiratory frequency and decrease in tidal volume were seen. These effects may be due to other properties of the drug, such as antagonism of substance P receptors (294) or inhibition of glutamic acid release (87).

Two "classical" GABA antagonists, bicuculline and picrotoxin (107), possess respiratory stimulant effects (148, 159, 216). Picrotoxin increased both respiratory rate and tidal volume by altering central respiratory rhythmicity (159). However, both drugs are difficult to study

as they have analeptic and convulsant actions on anesthetized animals. The stimulatory effects obtained, however, indicate that GABA-containing neurons may exert a tonic depressive influence on central neuronal populations involved in respiratory regulation.

In recent studies by our laboratories (145, 146), both GABA and the GABA-like drugs, GHBA and muscimol, depressed ventilation in preterm neonatal rabbits. These results may indicate that central GABA mechanisms may be involved in some forms of neonatal respiratory pathology. Interestingly, profound hypoxia, which is often associated with respiratory depression in the neonate, increases GABA levels in the brain stem area of newborn animals (155). These results may further strengthen the coupling of brain GABA mechanisms to neonatal respiratory dysfunction. Waldrop et al. (344) have observed that bicuculline prevented the long lasting (1 hr) inhibition of respiration that is produced by stimulation of limb muscles or their afferents.

The anatomical structures involved in the respiratory depressant effects of GABA have not yet been established. The evidence by Yamada et al. (364) suggests that the action of muscimol is exerted in the hindbrain of cats. GABA neurons located rostrally or caudally to the brainstem respiratory group of neurons may be involved, since GABA containing neurons have a widespread distribution within the CNS (290). Nevertheless, several workers have observed that GABA affects respiratory-related neurons directly. Denavit-Saubie and Champagnat (64, 94, 95) iontophoretically applied GABA to respiratory-modulated neurons in the pneumotaxic center region and medullary respiratory-related cells, while obtaining microelectrode recordings. In these spinal transected, vagotomized, paralyzed cats, these respiratory neurons were less sensitive than nonrespiratory neurons in the same general region, with more depression of neurons linked to the expiratory phase than of inspiratory neurons at similar injection currents (94). Moreover, inspiratory neurons in the ventral nucleus of the NTS and the nucleus ambiguus, as well as some neurons in the pneumotaxic center were depressed by GABA administration (94, 95).

Blockade of GABA uptake by iontophoretically administered nipecotic acid or β-alanine potentiated the depressant effects of subsequent GABA administration (64). Since endogenously originating expiratory inhibition of inspiratory neurons is antagonized by bicuculline and picrotoxin, and since both GABA and the normal endogenous inhibition are dependent on the chloride transmembrane gradient, Champagnat et al. (64) have suggested that GABA may play a role in determining the periodicity of firing of brain stem neurons that fire in inspiration. These findings would seem to agree with the earlier studies of Kirsten et al. (189). With midcollicular decerebrate, vagotomized, paralyzed, ventilated cats, GABA applied iontophoretically tended to inhibit both respiratory and nonrespiratory units, and units whose firing pattern spanned both inspiration and expiration reverted to firing in either one phase or the other (189). Similarly, Toleikis et al. (330) noted that in intact cats under Dial-urethane anesthesia, iontophoretic application of GABA depressed phasic firing of respiratory related neurons, whether firing in inspiration or expiration. Thus, perturbations of GABA availability may directly impact on central respiratory regulation.

In addition to direct actions, GABA may influence respiratory function by influencing the activity of other neural systems. In several publications by Carlsson and coworkers (60), GABA administration by various techniques has been shown to influence catecholamine- and serotonin-containing neurons in the rat brain. These, as well as other studies (128), indicate that GABA inhibits the firing of dopaminergic neurons in various parts of the brain (e.g. nigrostriatal, mesolimbic, and tubero-infundibular systems). Theoretically, if GABA influences respiratory-controlling mechanisms indirectly via a dopaminergic mechanism, dopamine receptor blocking drugs such as haloperidol would potentiate the depressant effects of GABA on respiration. Preliminary unpublished observations from our laboratory indicate that this is not the case, thus favoring the hypothesis that dopaminergic and gabaergic neurons act independently on respiratory-controlling mechanisms. Interactions of GABA with serotonin mechanisms (59) provide another route for indirect actions of GABA on respiratory mechanisms (34, 241). In contrast to the inhibitory effects on dopamine-containing neurons, GABA seems to facilitate transmitter release from epinephrine- and noradrenaline-containing neurons (60). The data of Fuxe and coworkers (128) indicate that local gabaergic mechanisms controlling such noradrenaline plexa may be located in the hypothalamic region. Several lines of evidence now suggest that both benzodiazepines and barbiturates interact with certain structures in the GABA receptor complex (17, 129). While such findings could explain the well known respiratory depressant effect of benzodiazepines and barbiturates, Bolme and Fuxe observed that picrotoxin could not antagonize the respiratory depressant effect of diazepam in intact chloralose-anesthetized rats (34).

VII. Glycine, β-Alanine, Taurine, Glutamate

Several amino acids that normally occur in relatively large amounts in the CNS are able to cause marked alterations in neural activity. Many of these amino acids, such as glycine, β-alanine, and taurine generally depress neuronal activity, and according to established criteria are accepted to have a neurotransmitter function within the CNS.

A. Glycine

Glycine administered intracisternally or i.c.v. has effects on many physiological systems such as the induction of a cataleptic-like state, delayed recovery of righting reflex, decreased body temperature, and arterial hypo-

tension (308). Respiratory depression, sometimes leading to a transient apnea, has also been described after intracisternal administration of glycine to diethylether-anesthetized rats by Sgaragli and Pavan (308). Similar responses were also observed after injection into the lateral ventricle in the halothane-anesthetized rat (150). In this latter preparation, glycine caused a depression of both respiratory frequency and tidal volume at lower doses than those reported to be effective by Sgaragli and Pavan. The effects of glycine in the halothane-anesthetized rat were immediate in onset, had a duration of at least 45 minutes and the respiratory response to CO_2 was abolished.

It is possible that the effects of glycine on respiration are elicited within the brain stem area, since electrophysiological experiments in this region have shown that glycine produces a potent hyperpolarizing effect (355) that can be reversed by strychnine (81). The effects of strychnine may be secondary to an antagonism at the glycine receptor since radiolabelled strychnine binds specifically to glycine-sensitive sites in brain stem and spinal cord (368). Hösli et al. (172) demonstrated that glycine also depressed the spontaneous firing of neurons in the bulbar reticular formation, an effect which also could be inhibited by strychnine (172). Toleikis et al. (330) found that iontophoretic application of glycine was less effective in depressing phasic activity in respiratory related neurons than was GABA. By measuring the electrical discharge in bulbar respiratory and nonrespiratory neurons in the cat, Denavit-Saubie and Champagnat (93) could demonstrate that glycine inhibited the discharge of bulbar neurons. However, respiratory units showed a higher "resistance" to this depressant amino acid compared to nonrespiratory related units. Strychnine is a powerful analeptic with respiratory stimulant effects even in animals not given exogenous glycine (346). Champagnat et al. (64) have recently suggested that the normal inhibitory input, which turns off inspiratory discharging neurons at the start of expiration, may involve one of the inhibitory compounds such as glycine, β-alanine or taurine (64). All of these are antagonized by strychnine administration. Both natural and glycine-induced inhibition are related to chloride-dependent hyperpolarization of the membrane (79). Thus, glycine-containing neurons may directly or indirectly exert a tonic inhibitory influence on the rhythmic oscillatory respiratory mechanisms in the brain stem.

B. β-Alanine

β-Alanine is an amino acid that is present in low concentrations in the mammalian CNS (272), and exerts a potent depressant effect on central neurons (82). β-Alanine has a regional distribution in the CNS similar to that of GABA (217), and like GABA and taurine, β-alanine depresses motor behavior and decreases body temperature (16, 175, 226).

Respiratory effects of β-alanine have been reported by Holzer and Hagmüller (169) who administered β-alanine systemically to pentobarbital-anesthetized rats. Transient apnea was seen after relatively high doses, and compared to GABA, β-alanine was considerably less potent. Intracerebroventricularly administered β-alanine induces a respiratory depression in doses comparable to those of glycine and GABA in the halothane-anesthetized rat (150). Like glycine, β-alanine induced an immediate depression of both respiratory frequency and tidal volume, and abolished the stimulatory effect of CO_2 on respiration. The respiratory effects of β-alanine are most probably elicited within the brain stem region. Supporting this is data from electrophysiological studies demonstrating that β-alanine depresses the spontaneous firing of brain stem neurons (172). In this electrophysiological investigation as well as in our respiratory study, the effects of glycine and β-alanine were similar. Furthermore, strychnine antagonized the depressant effects of both glycine and β-alanine on the spontaneous neuronal firing in the bulbar reticular formation (172). Taken together, these data may indicate that glycine and β-alanine act via similar mechanisms on respiration in the brain stem region.

C. Taurine

Taurine is an amino acid found in high concentrations and with a heterogenous distribution in the brain (16, 75). Iontophoretically applied taurine inhibits spontaneous firing of neurons in several regions in the CNS such as the spinal cord, brain stem, and cerebral cortex (80). This amino acid as well as β-alanine has been classified as glycine-like because of the susceptibility to antagonism by strychnine (81). Like GABA, glycine, and β-alanine, i.c.v. administration of taurine depresses motor behaviors and decreases body temperature (16, 175, 217). In the rat, i.c.v. administration of taurine induced a dose-dependent respiratory depression sometimes leading to a transient apnea (150). These effects have earlier been reported at similar doses by Sgaragli and Pavan (308). Our results indicate that taurine may be a more potent inducer of respiratory depression in the rat than glycine and β-alanine (150). In contrast to this, Holzer and Hagmüller (169) reported that taurine was less potent than β-alanine and GABA in inducing transient apnea (169). These authors used a peripheral route of administration which might explain the differences in results obtained.

Apart from glycine, β-alanine, and taurine, data from the literature indicate that other amino acids like α-alanine and *l*-serine may also exert a respiratory depressant action within the CNS (308).

D. Glutamate

The amino acid, L-glutamate, has been proposed as a putative neurotransmitter in several intrinsic pathways in the CNS (126, 313) and of dorsal root afferent fibers (179). Recently, L-glutamate has also been proposed to be a primary neurotransmitter in the NTS (327), producing hypotension, bradycardia, and apnea responses (155).

Kainic acid, an analogue of L-glutamate, elicited similar effects as L-glutamate when microinjected into the CNS (328). The responses to L-glutamate and kainic acid in the rat were restricted to the intermediate part of the NTS and could not be elicited by injections into adjacent sites in the brain stem (327, 328). Thus, signals in the afferent baroreceptor fibers or their relays to the respiratory, vasomotor, and cardioinhibitory centers may make use of glutamate release. An increased impulse activity of these fibers causes an inhibition of respiration (22, 72). The nodose ganglion contains the cell bodies of many of the arterial baroreceptor nerves as well as afferent fibers from pulmonary receptors (267, 287). Since extirpation of the nodose ganglion results in a degeneration of L-glutamate-containing nerves in the NTS, this amino acid may also function as a neurotransmitter in other afferent nerves to the NTS besides the baroreceptor nerves. Toleikis et al. (330) have shown that iontophoretic administration of glutamate was about equally effective as aspartic acid when applied to inspiratory or expiratory respiratory-related neurons. Berger and Cooney (21) have recently reported the effects of kainic acid-induced lesions of the ventrolateral NTS. It should be recalled that kainic acid selectively destroys neuronal soma that have glutamate receptors (260). Although the respiratory pattern in awake cats was not grossly changed, when anesthetized, a striking decrease in frequency and the tidal volume/inspiratory time ratio developed. Thus glutamate sensitive cells in the NTS may be important to maintaining normal ventilation during anesthesia.

Even though the putative amino acid neurotransmitters have to be administered in relatively high doses in order to induce respiratory effects, electrophysiological experiments indicate that they may be active in the brain stem during normal physiological circumstances. The need for very high doses may be due to poor penetration to relevant areas in the brain. The respiratory effects seem to be primary and not secondary to factors such as blood pressure changes and changes in thermoregulation (150). From available data it cannot be elucidated whether these amino acids act via specific receptor systems or indirectly via interactions with other neurotransmitters.

VIII. Effects of Peptides on Respiratory Activity

A. Thyrotropin-Releasing Hormone

1. Localization. The initial evidence that peptides were important in CNS function came from work demonstrating that peptides localized in the hypothalamus could influence the release of hormones from pituitary. The first of these factors isolated was thyrotropin-releasing hormone (TRH), which was identified as the tripeptide pyroglutamyl-histidyl-prolinamide (30, 54). Since these early investigations, more than a dozen other neuroactive peptides have been isolated from brain tissue and implicated in CNS function. Aspects of this rapidly expanding area of neurobiology are discussed in several recent reviews (166, 282, 312).

Approximately 70% of the total TRH in brain has been demonstrated to be present in areas of brain other than hypothalamus (360). Appreciable levels of TRH have been found in the brain stem, which after hypothalamus and thalamus has the third highest concentration per unit weight (259). This content did not change after hypothalamic de-afferentiation, which suggests that the cell bodies for these terminals are located outside the hypothalamus (52). While there has been controversy concerning the authenticity of immunoreactive TRH in these extrahypothalamic brain areas (108, 369), recent evidence seems to indicate the presence of authentic TRH in extrahypothalamic areas of the CNS (187). TRH-binding sites also occur in many brain areas outside the hypothalamus (55, 56).

For several years, our laboratory has focused on the biological activities of TRH. When this compound was first isolated, TRH was believed to function primarily in the control of thyrotropin release from the pituitary (38). However, subsequent investigations that defined behavioral effects of TRH suggested that it also had extrahypothalamic actions (44, 275, 360). This latter characterization provided the first evidence that releasing factors might have roles as neurotransmitters or neuromodulators distinct from their actions on the pituitary (43, 281). Recently, a functional differentiation of TRH receptor sites was suggested from work showing that administration of TRH into specific extrahypothalamic areas of the CNS resulted in antagonism of pentobarbital-induced narcosis, whereas injectio s into other sites were ineffective (183).

2. Respiratory Effects. In addition to its effects on temperature and increased locomotor activity (44), TRH has been shown to alter respiration (170, 194). Metcalf and Myers (230) suggested that TRH-induced tachypnea can be produced after mesencephalic reticular injection in intact cats and speculated that this response might explain the hypothermia noted in this species (229). The increase in minute ventilation after i.c.v. administration of TRH to halothane-anesthetized rats is not abolished by vagotomy, although in the vagotomized animal the change appears as an increase in tidal volume, not frequency (240). Yammamoto et al. (365) observed in newborn rabbits that the respiratory effects of TRH are abolished by decerebration at the midbrain level, and the peptide is inactive when applied to the floor of the fourth ventricle (365). These observations suggest that the TRH effect is exerted at the midbrain level, although higher areas may also be involved. In the rostral hypothalamus, local inhibitory effects of TRH are ultimately expressed as a respiratory stimulation (115). This recent observation in haloperidol-treated rats does not agree with the findings of Myers et al. (230) in awake intact cats, and probably is the result of the simultaneous presence of haloperidol.

In more recent studies of TRH effects on respiration in halothane-anesthetized rats (45, 147, 240), we have observed an increase in minute ventilation as a result of pronounced tachypnea with a fall in $PaCO_2$ after administration of 0.5 to 30 μg TRH into the lateral ventricle. Although one recognized metabolite of TRH, TRH acid, produced a small increase in basal and CO_2-stimulated respiration, a subsequent metabolite, the histidine-proline diketopiperazine, was inactive. The response to TRH acid developed more quickly than that seen after TRH, but higher doses were required for equivalent degrees of increase in minute ventilation. The peptide pyroglutamyl histidine-proline-glycinamide, a possible precursor of TRH, also produced respiratory stimulation similar to TRH, but it could not be determined whether this response was due to the parent tetrapeptide, or was due to subsequently synthetized TRH.

Hökfelt et al. (166) have reported that TRH occurs in serotonin-neurone-rich nuclei in the brain stem. Moreover, since 5,7-dihydroxytryptamine-treated rats have an elevated basal $PaCO_2$ whether awake or anesthetized, it is possible that TRH may be involved in normal modulation of respiratory activity. These animals also displayed a 3-fold increase in sensitivity to the respiratory effects of TRH. Neither serotonin depletion with *p*-chlorophenylalanine or pretreatment with methysergide altered the relative sensitivity to TRH. Atropine was unable to block the TRH response, whether given centrally or peripherally. Curiously, untreated animals given CO_2 to produce a $PaCO_2$ equivalent to that observed in 5,7-dihydroxytryptamine-treated rats before TRH also have an increased response to TRH. Thus, by altering the distribution of receptor affinity for TRH, CO_2 may alter the biological responses produced by TRH.

Hedner et al. (154), with newborn preterm rabbits anesthetized with halothane, noted that intraperitoneal TRH increased minute ventilation by an increase in frequency. An increase in inspiratory time/respiratory cycle length suggested that the response is the result of alterations in respiratory timing rather than inspiratory drive.

Evidence from a variety of neurobiological studies has suggested that some of the effects of TRH are mediated by interactions with several neurotransmitter systems in brain. The earliest studies demonstrated that TRH increased norepinephrine turnover without affecting amine content (43, 44, 171, 186). However, destruction of adrenergic fibers with 6-hydroxydopamine treatment did not alter the locomotor activity induced by TRH (338), and recent studies in our laboratory suggest that the respiratory stimulation is also unchanged. Thus, the observed biochemical change in noradrenergic mechanisms caused by TRH has not yet been related to specific physiological or behavioral actions.

Cott and Engel (77) proposed that the analeptic actions of TRH may be related to an inhibition of GABA function. In agreement with these earlier studies, Yarborough (366) confirmed that baclophen reduced TRH-induced tremor, antagonized the ability of TRH to decrease the sleep induced by CNS depressants, and prevented the elevated respiration caused by TRH in pentobarbital-treated rats. Interestingly, other GABA-mimetics, such as muscimol, did not alter these actions of TRH. Since there are questions concerning the mechanism of action of baclophen (see GABA section above), it is uncertain what the exact nature of TRH-GABA interactions may be.

In addition to the above description of TRH effects on respiration in 5,7-dihydroxytryptamine-treated rats, TRH dependent behavior may result from serotonin interactions. TRH is also believed to alter serotonergic receptor function, since it will potentiate the actions of 5-hydroxytryptophan and other serotonergic agonists (141).

Finally, considerable data have linked the effects of TRH to central cholinergic mechanisms. Thus, muscarinic-blocking drugs have been reported to abolish the actions of TRH to activate the EEG in rabbits (20) and to block the TRH-induced increase in glucose utilization in pentobarbital-treated rats (248). These findings suggest that the analeptic actions of TRH may be mediated through a cholinergic mechanism. In accord with this view, Schmidt (305) has shown that TRH reverses the decreased cholinergic activity caused by depressant drugs. Further, TRH is reported to reduce acetylcholine content and increase turnover in cortical regions (213) and to enhance the excitatory actions of acetylcholine on individual neurons (366). All these data suggest a modulatory role for TRH on synaptic processes involving cholinergic neurons. However, we have been unable to antagonize the effects of TRH on respiration with cholinergic antagonists (240).

While it is conceivable that some of the biological responses may be due to the release of TSH and ultimately thyroid hormones, the brain stem transection and microinjection experiments would seem to rule this out. With chronic administration of TRH or stable analogues, increased levels of thyroxin could be taken up into nerve terminals and mimic or modulate some of the classic neurotransmitters discussed above (99), although evidence for such a mechanism for respiratory changes after TRH is lacking.

In spite of the progress that has been made, until several questions are answered about mechanism of synthesis, storage, release, and inactivation of TRH, it will be difficult to solidly implicate TRH in respiratory mechanisms. Furthermore, physiological studies would be greatly facilitated if a specific antagonist of TRH actions were available. Controversy still exists about active metabolites of TRH and the methods by which TRH can be measured in tissue. Future investigations must resolve these difficulties in order to facilitate our understanding of the role of TRH in brain function in general and respiratory control in particular.

B. Substance P

1. Localization. Substance P (SP) is a peptide that was first described by von Euler and Gaddum in 1931 (342). The amino acid sequence of SP, H-ARG-PRO-LYS-PRO-GLY-GLY-PHE-PHE-GLY-LEU-MET-NH_2, was established in 1971 (65). Recent research has demonstrated a widespread distribution of SP-containing neurons in the rat CNS (161, 251). Both SP-containing cell bodies as well as terminals are found in several brain stem regions such as the periventricular central gray, raphe nuclei, gigantocellular reticular nucleus, nucleus commisuralis, LC, and nucleus dorsalis nerve vagi. Pathways containing SP (109) and regional localization of receptors (249) have been demonstrated, even though the biosynthesis and inactivation of SP have not yet been characterized. Virtually all neurons that are affected by SP are excited and the excitation has been shown to be associated with depolarization (251). However, it has not been possible to rigorously compare the membrane effects of SP with the synaptic potentials that are presumed to be mediated by SP (251). Thus, although the evidence for a classical neurotransmitter role for SP is very strong, this has so far not been proven. It has been proven that SP plays a role in nociceptive primary afferent sensory neurons (161, 203) and afferent baroreceptor neurons (135, 140, 144, 157, 337).

2. Respiratory effects. In 1956 von Euler and Pernow (343) reported that intracisternal and i.c.v. injections in rabbits and cats caused a dose-dependent increase in both respiratory frequency and amplitude. In our laboratory we have studied the effects of i.c.v.-administered SP on respiratory regulation in the intact, halothane-anesthetized rat. SP induced a selective dose-dependent increase in V_T but had no effect on f (152) and (Mueller et al., unpublished observations). The effects had a short onset and were slowly returned to normal within 30 minutes. Thus, minute ventilation was increased, accompanied by a decrease in $PaCO_2$ and an augmented mechanical response to CO_2 exposure. We have also observed a slight increase in mean arterial blood pressure after this route of administration. This effect has also been described by Haeusler and Osterwalder (144), who, in addition, noted hypotension and bradycardia after local application in the region of the NTS (144). Other authors have described a hypertensive action of SP in the NTS (140) while Talman and Reis (329) have argued that these actions in the NTS could be a consequence of local distortion of the tissue at the injection site. Recently, Yammamoto et al. (365) applied SP directly onto the exposed surface of the medulla of decerebrate rabbit pups and registered a respiratory pattern similar to the one described above, which indicates a site of action within the brain stem area. Furthermore the SP response was potentiated after naloxone pretreatment which would be in accordance with earlier findings that SP release is inhibited by opiate analgesics (178).

A major deficiency in SP research has been the absence of a specific SP antagonist. Recently, however, new analogues of SP (D-Pro^2, D-Phe^7, D-Trp^9)-SP and (D-Pro^2, D-$Trp^{7,9}$)-SP, have been synthesized and found to block peripheral effects of SP (125, 292). The analogue (D-Pro^2, D-$Trp^{7,9}$)-SP has been shown to antagonize the excitatory effect of SP on single cells in the LC (110). No complete studies concerning the respiratory effects of this latter antagonist have yet been made; however, preliminary results from our laboratory have shown a respiratory stimulation at lower doses followed by apnea at higher doses (Hedner et al., unpublished observations). Perhaps this antagonist also possesses some partial agonist activity, which is visible at low doses.

3. Physiological-pathological interactions. Another potential way to explore the importance of SP in respiratory control is to use the toxin capsaicin (8-methyl-N-vanillyl-6-nonenamide). This pungent and irritating compound occurs naturally in peppers of the genus Capsicum, including Mexican chile pepper and Hungarian red pepper (paprika). Initially after application of capsaicin SP is released from the spinal cord (362). However, systemic administration of capsaicin results in a long-lasting reduction of the SP content in regions that contain primary sensory neurons (130). This nerve terminal destruction seems to be irreversible if the drug is given within the first 10 days of life.

It has long been known that i.v. administration of capsaicin to dogs induces an immediate apnea, followed after 20 seconds by a tachypnea and these effects can be reversed by cooling of the vagi nerves (279). Coleridge et al. (73) showed an increase in V_T and f after i.v. administration of capsaicin in the vagotomized dog. Thus it is possible that capsaicin, and perhaps subsequently released SP, can affect respiration by acting on peripheral chemoreceptors and by altering the activity in centrally located SP neurons. Early treatment with capsaicin to deplete centrally (and peripherally) located SP-containing neurons might be a valuable tool in the research on SP actions on central respiratory regulation. However, the possibility that the respiratory changes seen after capsaicin might be secondary to perturbation of other peptides like somatostatin (131), remains to be elucidated. In preliminary experiments, we have registered SP-like effects directly after i.c.v. capsaicin administration. Animals treated at 5 days of age with capsaicin showed a decrease in brain stem SP levels and an increased basal respiratory frequency as well as an increase in f as a response to i.c.v. SP injection (Hedner et al., unpublished observations). In adult rats treated with subcutaneous capsaicin the minute ventilation response to i.c.v. SP is unaltered, nor is the mechanical response to acute vagotomy changed (Mueller et al., unpublished observations).

Since SP coexists with serotonin in several brain stem neurons, it is possible that the hypoventilation that follows destruction of serotonergic neurons with neonatal

administration of 5,7-dihydroxytryptamine might be a consequence of decreased availability of this peptide. Although we have been unable to test this directly, rats treated neonatally with 5,7-dihydroxytryptamine alone or in combination with capsaicin do not have an increased sensitivity to i.c.v. SP (Mueller et al., unpublished observations).

C. Enkephalin/Endorphins/Narcotic Analgesics

1. Localization. Since the discovery in 1976 of endogenous opioid peptides in brain (40, 204), enkephalins and endorphins have been identified in several areas of the CNS. Based on present knowledge, it appears that at least three distinctly different systems can be identified in the brain: a.) β-endorphin neurons, with cell bodies in the medial part of the hypothalamus and axons spreading anteriorly and cranially toward nucleus accumbens and septal areas and further on to the thalamus, periaqueductal gray, and LC (29); b.) enkephalin neurons appearing in more than 30 different areas of the brain either as local cell groups or short fiber systems (162, 331); and, c.) dynorphin neurons, with cell groups in the hypothalamus and projections most probably to the posterior part of the pituitary (136). The distribution of the two pentapeptides, met-enkephalin and leu-enkephalin, seems to be similar and they may even occur within the same neuron, (102); among other regions of the brain stem, met-enkephalin immunoreactive cell bodies were observed in the parabrachial nuclei and the NTS.

Different types of opiate receptors (μ, κ, σ) were first postulated by Martin et al. (218). After these initial observations their theory has been modified and other receptor types like δ-, ϵ-, and dynorphin receptors have been described [see e.g. Miller (232)]. In order to propose endogenous peptides as agonists on specific receptor types, the following scheme has been suggested: enkephalins,-δ receptor; β-endorphin,-ϵ receptor; and dynorphin,-κ receptor. An endogenous ligand for some receptors has not been defined, but this may not be necessary if the theory by Pert and coworkers (37) is correct, i.e., δ and μ receptors may be two convertible forms of the same structure. High concentrations of opiate receptors as well as enkephalins are found in the solitary nuclei and other medullary areas that may house the basic respiratory oscillator or are considered to be important relay stations for a variety of chemical and sensory stimuli which affect ventilation (10, 11, 22). These observations have led several investigators to look for an effect of endogenous opioids on ventilatory control.

2. Respiratory effects. Before the current studies of alterations induced by endorphins and enkephalins began, many respiratory studies were performed with the opiate analgesics. Since opiate analgesics bind to the same receptor sites in the brain as the endogenous opioid peptides, one can draw inferences about the function of these receptors from studies with more classic agonists. From experiments in animals, morphine has been demonstrated to have essentially independent actions on the frequency and tidal volume control mechanisms of the respiratory center (36) in addition to its ability to depress the peripheral hypoxic drive to respiration (351). This was pointed out by Cushny (83) and it has subsequently been found that almost the entire decrease in total ventilation arises from the relative failure of the respiratory center to respond fully to CO_2 (36). From the early studies on morphine it also appeared evident that morphine does not act simply by blocking vagal inputs to the respiratory center (83). Some neurophysiological stimulation experiments have shown that the electrically evoked maximal respiratory efforts produced by stimulation in the medulla oblongata were not affected by opiate drug treatment (120, 133, 250). Other experiments have demonstrated an increased threshold for electrical excitation of the medullary center, which suggests that opiates may act in part by adjusting threshold excitability at the medullary level (36). Recently, new narcotic analogues have been introduced that appear to have a limit in the amount of respiratory depression they produce (137, 184). Whether this ceiling effect is due to antagonist properties that became apparent at higher doses or nonspecific CNS excitation as the dose is increased is still not clear.

From the early studies by Moss and Friedmann (239) it was known that endogenous opioid peptides depress ventilation. Florez et al. (122) used i.c.v. injections in cats and found that met-enkephalin induced a short-lasting respiratory depression when applied to the ventral surface of the brain stem of lightly anesthetized animals. The short duration of the response was proposed to be the result of rapid inactivation of this compound, in reasonable agreement with the ability of met-enkephalin to induce analgesia in experimental animals (1). Extended studies on synthetic enkephalin analogues and β-endorphin demonstrated longer actions of these compounds after injection into the lateral ventricles in cats, also in agreement with their actions on other physiological variables following administration into brain (1, 122). Injection of met-enkephalin and β-endorphin into the lateral ventricle of lightly anesthetized cats acted to depress ventilation at higher brain structures while met-enkephalin but not β-endorphin affected respiration when applied to the pontomedullary surface of the brain stem (122). Zobrist et al. (371) observed that (D-ala^2) methionine-enkephalinamide exerted effects on respiration similar to those of morphine, and that tolerance induced by morphine or the peptide produced cross tolerance to the respiratory depressant effects. The respiratory depression induced by the endogenous opioids and their analogues was reversed with the opiate antagonist naloxone (122). These observations are consistent with work demonstrating that respiratory depression accompanies various conditions associated with increased endogenous opioid activity. From the numerous investigations with endogenous opioids and exogenous opiates it

is evident that the respiratory depressant effects of this group of agents cannot be confined to a single receptor site but can be registered after activation of several of the receptor subtypes listed above. Oktay et al. (258) recently reported that the depressant effect of morphine on respiratory frequency in awake mice is potentiated by the protease inhibitor captopril. Although these results could be due to an effect of captopril on the pharmacokinetics of morphine or changes in morphine receptors, it is also possible that morphine promotes the release of endogenous peptides.

Pokorski et al. (278) observed that application of a morphine receptor agonist, fentanyl, to the intermediate chemosensory integration area (area S) of the ventrolateral cat medulla depressed the phrenic electroneurogram in spontaneously breathing cats anesthetized with pentobarbital; naloxone produced an opposite response. Placement of these compounds on the caudal chemosensitive zone (area L) was without effect. In contrast, Hurlé et al. (176) have reported that in pentobarbital-urethane anesthetized intact cats, the rostral chemosensitive area M was more sensitive than area S to the depressant effect of morphine. The discrepancy between the Pokorski et al. and Hurlé et al. data may represent a difference between the L and M chemosensitive sites, but more probably reflect the different effects of unbuffered alkaloid solutions in which the more concentrated morphine would exert a more robust effect. Other brain stem neurons related to respiration also appear sensitive to direct opioid application. Denavit-Saubie et al. (96) observed a depression of spontaneous discharge of pontine and medullary respiration neurons after application of enkephalin.

Some animal studies have been presented that imply that endogenous opioids may modulate normal respiratory drive. Naloxone has been shown to increase phrenic nerve output in cats deprived of respiratory chemical feedback (200). In the rabbit, naloxone augments carbon dioxide-induced stimulation of minute volume (23). Waldrop et al. (344) have recently shown that the long-lasting inhibition of respiratory output that occurs after stimulation of limb muscles or their afferents in anesthetized, paralyzed, vagotomized, and carotid sinus denervated cats can be antagonized by naloxone. Recently, however, it has been reported that naloxone antagonized respiratory depression produced by the adenosine agonist, 2-chloroadenosine (245). Perhaps the responses observed after naloxone in animal studies reflects tissue damage and adenosine release during preparation of the animal for study. Alternatively, adenosine agonists may promote the increased release of endogenous opioids. In the human adult, diverging data on the effects of naloxone exist; two studies showed unaltered ventilatory responses to hypoxemia and hypercapnia after large doses (10–50 mg) of naloxone (119, 182) while another study on patients with chronic obstructive pulmonary disease reported an increased ability to compensate for an additional respiratory load after naloxone administration (299).

3. Physiological-pathological interactions. In the human, the respiratory depression demonstrated in necrotizing encephalomyelopathy is accompanied by increased CSF and brain endorphin levels, and is antagonized by naloxone (41). In rats, Holaday and Faden (167) observed that bradypnea after spinal cord trauma was effectively reversed by naloxone.

In the neonate, several reports indicate that enkephalins and endorphins can influence respiratory function. In a recent study, we demonstrated that a stable enkephalin-analogue induced a marked respiratory depression in neonatal rabbits (153). This effect could be rapidly antagonized by naloxone. Moreover, some studies in neonatal rabbits indicated that endogenous opioids may be involved in the depressed ventilation seen during asphyxia or severe CNS hypoxemia. For example, asphyxiated fetal rabbits whose mothers had received naloxone were less depressed at birth than the offspring of placebo-treated animals (69, 70). Furthermore, the characteristic ventilatory depression caused by severe hypoxemia in the neonatal rabbit could be reversed by naloxone (142, 225). These observations may be of interest in human pathological states since plasma β-endorphin levels are elevated at birth in the human fetus, and the highest concentrations are found when the fetus is hypoxemic (347). In contrast, during another form of respiratory abnormality in human infants, apnea of prematurity, naloxone does not abolish the respiratory irregularity noted in this condition (69), which suggests that endogenous opioids are not involved in this form of respiratory pathology. Curiously, offspring of mothers who chronically consume methadone evidence a decreased sensitivity to CO_2 relative to controls for as long as 31 days after delivery. This altered sensitivity to CO_2 may contribute to increased apneic spells in these infants (261).

The respiratory depression after endogenous and exogenous opioids may be partly mediated through other neurotransmitter systems. Supporting this is the recent study by Meldrum and Isom (225) where the respiratory response to morphine could be altered by agents affecting central noradrenaline and serotonin concentrations. Drugs that increased brain 5-HT content potentiated the morphine-induced respiratory depression while agents increasing brain norepinephrine concentration antagonized this effect of morphine; this suggests that these amines modulate the effect of opioid receptor stimulation. In addition, Weinstock et al. (353) noted that the central cholinesterase inhibitor physostigmine could reverse the respiratory depressant (elevated $PaCO_2$) effect of morphine in conscious rabbits. Since this drug does not antagonize the analgesia produced by morphine (90), this finding could have clinical importance.

Yaksh et al. (363) have demonstrated that the application of narcotic analgesics to the lumbar intrathecal

space produce a localized segmental analgesia, and this technique has now been successfully employed for pain relief in man (297). Ventilatory depression appears to develop only slowly as the drug spreads cephalad, with maximal changes occurring at 6 hours after administration (191). These effects could be due to an action on spinal cord motor neurons (314), but are more probably the result of actions directly on the brain stem (191).

Several experimental lines of evidence support the view that endogenous opioids may play a functional role in normal breathing as well as several forms of respiratory pathology. However, demonstration of altered opioid peptide release or turnover in pathological respiratory states will be required before a basic role for these peptides in respiratory control can be unequivocally accepted.

IX. Concluding Remarks

From the many studies that have been reviewed in this manuscript, it is apparent that drug-induced changes in respiration depend upon the state of arousal (or anesthetic used) and the site at which the drug is injected. Thus opposite effects have been described for pharmacological manipulations of serotonin, dopamine, norepinephrine, and even GABA depending on experimental conditions. Although some disparate results may be secondary to different species used, one must acknowledge more similarities than differences between species.

Two conflicting points of view continue to hamper this research area. It would be most desirable for new therapeutic agents that affect respiration in man to be active after oral, or at least systemic, routes of administration. Conversely, to understand the basic neurobiology of respiratory control in the CNS, the drug should be administered to a localized area of brain; this permits the best definition of physiological inputs and modulating systems. Both approaches must be pursued to efficiently develop new therapeutic agents.

At present, medicine possesses a host of devices to quantify respiratory activity, and these have been of great help in evaluating the progression and response to therapy of a variety of pulmonary diseases. If it is presumed that neurotransmitter systems modulate respiration, perhaps respiratory measurements can tell us something of altered neurotransmitter function in neurological and psychiatric disease states, as well as changes in these conditions after therapeutic interventions. The tremendous inter-individual variability of mechanical indices of respiratory function are widely known. On the other hand, variability of many physiological parameters is an essential requirement for geneticists seeking to unravel the mysteries of trait inheritance. Perhaps more effort should be devoted toward discerning the basis of this variability, and its relationship to CNS neurotransmitters, rather than trying to use only experimental designs that minimize the effect of inter-individual respiratory variation.

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REFERENCES

1. Adler, M. W.: Minireview. Opioid peptides. Life Sci. **26:** 497–510, 1980.
2. Aghajanian, G. K., and Wang, R. Y.: Habenular and other midbrain raphe afferents demonstrated by a modified retrograde tracing technique. Brain Res. **122:** 229–242, 1977.
3. Aghajanian, G. K., and Wang, R. Y.: Physiology and pharmacology of central serotonergic neurons. *In* Psychopharmacology. A Generation of Progress, ed. by M. A. Lipton, A. DiMascio, and K. F. Killam, pp. 171–183, Raven Press, New York, 1978.
4. Aghajanian, G. K., Wang, R. Y., and Baraban, J.: Serotonergic and nonserotonergic neurons of the dorsal raphe: Reciprocal changes in firing induced by peripheral nerve stimulation. Brain Res. **153:** 169–175, 1978.
5. Andrews, P. R., and Johnston, G. A. R.: Commentary: GABA agonists and antagonists. Biochem. Pharmacol. **28:** 2697–2702, 1979.
6. Arkinstall, W. W., Nirmel, K., Klissouras, V., and Milic-Emil, J.: Genetic differences in the ventilatory response to CO_2. J. Appl. Physiol. **36:** 6–11, 1974.
7. Armijo, J. A., and Florez, J.: The influence of increased brain 5-hydroxytryptamine upon the respiratory activity of cats. Neuropharmacology **13:** 977–986, 1974.
8. Armijo, J. A., Mediavilla, A., and Florez, J.: Inhibition of the activity of the respiratory and vasomotor centers by centrally administered 5-hydroxytryptamine in cats. Rev. Esp. Fisiol. **36:** 219–227, 1979.
9. Aston-Jones, G., and Bloom, F. E.: Norepinephrine containing locus coeruleus neurons in behaving rats exhibit pronounced responses to nonnoxious environmental stimuli. J. Neurosci. **1:** 887–900, 1981.
10. Atweh, S. F., and Kuhar, M. J.: Autoradiographic localization of opiate receptors in rat brain. 1. Spinal cord and lower medulla. Brain Res **124:** 53–67, 1977.
11. Atweh, S. F., and Kuhar, M. J.: Autoradiographic localization of opiate receptors in rat brain. II. The brain stem. Brain Res. **129:** 1–12, 1977.
12. Bainbridge, C. W., and Heistad, D. D.: Effect of haloperidol on ventilatory responses to dopamine in man. J. Pharmacol. Exp. Ther. **213:** 13–17, 1980.
13. Baker, H., Joh, T. H., and Reis, D. J.: Genetic control of number of midbrain dopaminergic neurons in inbred strains of mice: Relationship to size and neuronal density of the striatum. Proc. Natl. Acad. Sci. U.S.A. **77:** 4369–4373, 1980.
14. Baker, T. L., and McGinty, D. J.: Reversal of cardiopulmonary failure during active sleep in hypoxic kittens: Implication for sudden infant death. Science **198:** 419–421, 1977.
15. Baldessarini, R. J., Amatruda, T. T., Griffith, F. F., and Gerson, S.: Differential effects of serotonin on turning and stereotypy induced by apomorphine. Brain Res. **93:** 158–163, 1975.
16. Barbeau, A., Tsukada, Y., and Inoue, N.: Neuropharmacologic and behavioral effects of taurine. *In* Taurine, ed. by R. Huxtable and A. Barbeau, pp. 253–266, Raven Press, New York, 1976.
17. Barker, J. L., and Mathers, D. A.: GABA receptors and the depressant action of pentobarbital. Trends Pharmacol. Sci. **2:** 10–13, 1981.
18. Barruzzi, A., Cirignotta, F., Coccagna, G., Calderini, G., and Lugaresi, E.: Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid in hypersomnia with periodic apneas or idiopathic hypersomnia: Preliminary results. Sleep **3:** 247–249, 1980.
19. Baxter, D. W., and Olszewski, J.: Respiratory responses evoked by electrical stimulation of pons and mesencephalon. J. Neurophysiol. **18:**276–287, 1955.
20. Beale, J. S., White, R. P., and Huang, S. P.: EEG and blood pressure effects of TRH in rabbits. Neuropharmacology **16:** 449–506, 1977.
21. Berger, A. J., and Cooney, K. A.: Ventilatory effects of kainic acid injection of the ventrolateral solitary nucleus. J. Appl. Physiol. **52:** 131–140, 1982.
22. Berger, A. J., Mitchell, R. A., and Severinghaus, J. W.: Regulation of respiration (Parts I–III) N. Engl. J. Med. **297:** 92–97, 138–143, 194–201, 1977.
23. Beubler, E.: Naloxone increases carbon dioxide stimulated respiration in the rabbit. Naunyn-Schmiedebergs Arch. Pharmakol. **311:** 199–203, 1980.
24. Bhattacharyya, N. K., Cunningham, D. J., Coode, R. C., Hawson, R. C., and Lloyd, B. B.: Hypoxia ventilation, PCO_2 and exercise. Respir. Physiol. **9:** 329–347, 1970.
25. Birkmayer, W. (ed.): Spasticity—A topical survey. Hans Huber Publisher, Bern, 1972.
26. Bjorklund, A., Falck, B., and Stenevi, U.: Classification of monoamine neurones in the rat mesencephalon: Distribution of a new monoamine neurone system. Brain Res. **32:** 269–285, 1971.
27. Black, A. M. S., Comroe, J. H., Jr., and Jacobs, L.: Species difference in

carotid body response of cat and dog to dopamine and serotonin. Am. J. Physiol. **223:** 1097–1102, 1972.
28. Bliss, E. L., and Ailion, J.: Relationship of stress and activity to brain dopamine and homovanillic acid. Life Sci. **10:** 1161–1169, 1971.
29. Bloom, F. E., Battenberg, E., Rossier, J., Ling, N., and Guillemin, R.: Neurones containing β-endorphin in rat brain exist separately from those containing enkephalin: Immunocytochemical studies. Proc. Natl. Acad. Sci. U.S.A. **75:** 1591–1595, 1978.
30. Bohler, J., Enzmann, F., Folkers, K., Bowers, C. Y., and Schally, A. V.: The identity of chemical and hormonal properties of the thyrotropin releasing hormone and pyroglutamyl-histidyl-proline amide. Biochem. Biophys. Res. Commun. **37:** 705–710, 1969.
31. Bohmer, G., Dinse, H. R. O., Fallert, M., and Sommer, T. J.: Microelectrophoretic application of agonists of putative neurotransmitters onto various types of bulbar respiratory neurons. Arch. Ital. Biol. **117:** 13–22, 1979.
32. Bolme, P., Corrodi, H., Fuxe, K., Hokfelt, T., Lidbrink, P., and Goldstein, M.: Possible involvement of central adrenaline neurons in vasomotor and respiratory control. Studies with clonidine and its interactions with piperoxane and yohimbine. Eur. J. Pharmacol. **28:** 89–94, 1974.
33. Bolme, P., and Fuxe, K.: Pharmacological studies on a possible role of central noradrenaline neurons in respiratory control. J. Pharm. Pharmacol. **25:** 351–352, 1973.
34. Bolme, P., and Fuxe, K.: Possible involvement of GABA mechanisms in central cardiovascular and respiratory control. Studies on the interactions between diazepam, picrotoxin, and clonidine. Med. Biol. **55:** 301–309, 1977.
35. Bolme, P., Fuxe, K., Hökfelt, T., and Goldstein, M.: Studies on the role of dopamine in cardiovascular and respiratory control: Central versus peripheral mechanisms. Adv. Biochem. Psychopharmacol. **16:** 281–290, 1977.
36. Borison, H. L.: Central nervous respiratory depressants—Narcotic analgesics. J. Pharm. Ther. **3:** 227–237, 1977.
37. Bowen, W. D., Gentleman, S., Herkeham, M., and Pert, C. B.: Interconverting μ and δ forms of the opiate receptor in rat striatal patches. Proc. Natl. Acad. Sci. U.S.A. **78:** 4818–4822, 1981.
38. Bowers, C. Y., Friesen, H. G., Hwang, P., Guyda, H. J., and Folkers, K.: Prolactin and thyrotropin release in man by synthetic pyroglutamyl-histidyl-prolinamide. Biochem. Biophys. Res. Commun. **45:** 1033–1041, 1971.
39. Boyd, T. E., and Maaske, C. A.: Vagal inhibition of inspiration and accompanying changes of respiratory rhythm. J. Neuropharmacol. **2:** 533–542, 1939.
40. Bradbury, A. F., Smyth, D. G., and Snell, C. R.: Lipotropin: Precursor to two biologically active peptides. Biochem. Biophys. Res. Commun. **69:** 950–956, 1976.
41. Brandt, N. J., Terenius, L., Jacobsen, B. B., Klinken, L., Nordius, A., Brandt, S., Blegvad, K., and Yssing, M.: Hyper-endorphin syndrome in a child with necrotizing encephalomyelopathy. N. Engl. J. Med. **303:** 914–916, 1980.
42. Breese, G. R., Cooper, B. R., and Mueller, R. A.: Evidence for involvement of 5-hydroxytryptamine in the actions of amphetamine. Br. J. Pharmacol. **52:** 307–314, 1974.
43. Breese, G. R., Cooper, B. R., Prange, A. J., Cott, J. M., and Lipton, M. A.: Interactions of thyrotropin releasing hormone with centrally acting drugs. *In* The Thyroid Axis, Drugs, and Behavior, ed. by A. J. Prange, pp. 115–127. Raven Press, New York, 1974.
44. Breese, G. R., Cott, J. M., Cooper, B. R., Prange, A. J., Jr., Lipton, M. A., and Plotnikoff, N. P.: Effects of thyrotropin-releasing hormone (TRH) on the actions of pentobarbital and other centrally acting drugs. J. Pharmacol. Exp. Ther. **193:** 11–22, 1975.
45. Breese, G. R., Kilts, C. D., Beaumont, K., and Mueller, R. A.: Effect of 5,7-dihydroxytryptamine (5,7-DHT) on brain thyrotropin-releasing hormone (TRH) and the respiratory response to TRH. Soc. Neurosci. Abstr. **7:** 942, 1981.
46. Breese, G. R., Mueller, R. A., Mailman, R. B., and Frye, G. D.: Effects of TRH on central nervous system function. *In* The Role of Peptides and Aminoacids as Neurotransmitters, ed. by J. B. Lombardini and A. D. Kenny, pp. 99–116, Alan R. Liss, Inc., New York, 1981.
47. Breese, G. R., and Traylor, T. D.: Effect of 6-OHDA on brain norepinephrine and dopamine: Evidence for selective degeneration of catecholamine neurons. J. Pharmacol. Exp. Ther. **174:** 413–420, 1970.
48. Breese, G. R., Vogel, R. A., Kuhn, C. M., Mailman, R. B., Mueller, R. A., and Schanberg, S. M.: Behavioral and prolactin responses to 5-hydroxytryptophan in rats treated during development with 5,7-dihydroxytryptamine. Brain Res. **155:** 263–275, 1978.
49. Briscoe, J. J., and Purves, M. J.: Factors affecting the cat carotid chemoreceptor and cervical sympathetic activity with special reference to passive hind-limb movements. J. Physiol. (Lond.) **14:** 102–104, 1967.
50. Brodie, B. B., and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Ann. N.Y. Acad. Sci. **66:** 631–642, 1957.
51. Brown, R. M., Kehr, W., and Carlsson, A.: Functional and biochemical aspects of catecholamine metabolism in brain under hypoxia. Brain Res. **85:** 491–509, 1975.
52. Brownstein, M. J., Utiger, R. D., Palkovits, M., and Kizer, J. S.: Effect of hypothalamic deafferentation on thyrotropin-releasing hormone levels in rat brain. Proc. Natl. Acad. Sci. U.S.A. **72:** 4177–4179, 1975.
53. Bulat, M.: On the origin of 5-hydroxyindoleacetic acid in the lumbar cerebrospinal fluid. Brain Res. **122:** 388–391, 1977.
54. Burgus, R., Dunn, T. F., Desiderio, D., Ward, D. N., Vale, W., and Guillemin, R.: Characterization of ovine, hypothalamic hypophysiotropic TSH releasing factor. Nature (Lond.) **226:** 321–325, 1970.
55. Burt, D. R., and Snyder, S. H.: Thyrotropin-releasing hormone (TRH): Apparent receptor binding in rat brain membranes. Brain Res. **93:** 309–328, 1975.
56. Burt, D. R., and Taylor, R. L.: Binding sites for thyrotropin-releasing hormone in sheep nucleus accumbens resemble pituitary receptors. Endocrinology **106:** 1416–1423, 1980.
57. Byrne-Quinn, E., Weil, J. V., Sodal, I. E., Filley, F. G., and Grover, R. F.: Ventilatory control in the athlete. J. Appl. Physiol. **30:** 91–98, 1971.
58. Carlsson, A.: Receptor-mediated control of dopamine metabolism. *In* Pre- and Post-Synaptic Receptors. ed. by E. Usdin and W. E. Bunney, pp. 49–65, Marcel Dekker, New York, 1975.
59. Carlsson, A., and Biswas, B.: Effects of GABA administered intracerebroventricularly or intraperitoneally on brain monoamines and locomotor activity. *In* Interactions between Putative Neurotransmitters in the Brain, ed. by S. Garrattini, J. F. Pujol, and R. Samanin, pp. 305–315, Raven Press, New York, 1978.
60. Carlsson, A., Biswas, B., and Lindquist, M.: Influence of GABA and GABA-like drugs on monoaminergic mechanisms. *In* Advances in Biochemical Psychopharmacology, ed. by E. Costa and G. L. Gessa, vol. 16, pp. 471–475, Raven Press, New York, 1977.
61. Carlsson, A., Holmin, T., Lindqvist, M., and Siesjo, B. K.: Effect of hypercapnia and hypocapnia on tryptophan and tyrosine hydroxylation in rat brain. Acta Physiol. Scand. **99:** 503–509, 1977.
62. Casey, D. E., and Rabins, P.: Tardive dyskinesia as a life threatening illness. Am. J. Psychiatry **135:** 486–488, 1978.
63. Champagnat, J., Denavit-Saubie, M., Henry, J. L., and Leviel, V.: Catecholaminergic depressant effects on bulbar respiratory mechanisms. Brain Res. **160:** 57–68, 1979.
64. Champagnat, J., Denavit-Saubie, M., Moyanova, S., and Rondouin, G.: Involvement of amino acids in periodic inhibitions of bulbar respiratory neurons. Brain Res. **237:** 351–365, 1982.
65. Chang, M. M., Leeman, S. E., and Niall, H. D.: Aminoacid sequence of substance P. Nature New Biol. **232:** 86–87, 1971.
66. Chan-Palay, V.: The paratrigeminal nucleus. II. Identification and interrelations of catecholamine axons, indolamine axons, and substance P immunoreactive cells in the neuropil. J. Neurocytol. **7:** 419–442, 1978.
67. Chemerinski, E., Ramirez, A. J., and Enero, M. A.: Sinoaortic denervation induced changes in central serotonergic neurons. Eur. J. Pharmacol. **64:** 195–198, 1980.
68. Cherniack, N. S., Von Euler, C., Homma, I., and Kao, F. F.: Graded changes in central chemoceptor input by local temperature changes on the ventral surface of medulla. J. Physiol. (Lond.) **287:** 191–211, 1979.
69. Chernick, V., and Craig, R. J.: Endogenous opiates cause neonatal depression following fetal asphyxia. Pediatr. Res. **15:** 654, abstr. 1267, 1981.
70. Chernick, V., Madansky, D. L., and Lawson, E. E.: Naloxone decreases the duration of primary apnea with neonatal asphyxia. Pediatr. Res. **14:** 357–359, 1980.
71. Clineschmidt, B. V., and Anderson, E. G.: The blockade of bulbospinal inhibition by 5-hydroxytryptamine antagonists. Exp. Brain Res. **11:** 175–186, 1970.
72. Cohen, M. I.: Neurogenesis of respiratory rhythm in the mammal. Physiol. Rev. **59:** 1105–1173, 1979.
73. Coleridge, H. M., Coleridge, J. C. G., and Kidd, C.: Role of the pulmonary arterial baroreceptors in the effects produced by capsaicin in the dog. J. Physiol. (Lond.) **170:** 272–285, 1964.
74. Coles, D. R., Duff, F., Shepherd, W. H. T., and Whelan, R. F.: The effect on respiration of infusions of adrenaline, and noradrenaline into the carotid and vertebral arteries in man. Br. J. Pharmacol. **11:** 346–350, 1956.
75. Collins, G. G. S.: The rates of synthesis, uptake and disappearance of [^{14}C]-taurine in eight areas of the rat central nervous system. Brain Res. **76:** 447–459, 1974.
76. Cools, A. R., and van Rossum, J. M.: Minireview: Multiple receptors for brain dopamine in behavior regulation: Concept of dopamine-E and dopamine-I receptors. Life Sci. **27:** 1237–1253, 1980.
77. Cott, J., and Engel, J.: Antagonism of analeptic activity of thyrotropin releasing hormone (TRH) by agents which enhance GABA transmission. Psychopharmacology **52:** 145–149, 1977.
78. Cramer, H., Warter, J. M., Renaud, B., Krieger, J., Marescaux, C. H. R., and Hammers, R.: Cerebrospinal fluid adenosine 3′,5′-monophosphate, 5-hydroxyendoleacetic acid and homovanillic acid in patients with sleep apnea syndrome. J. Neurol. Neurosurg. Psychiatry **44:** 1165–1167, 1981.
79. Curtis, D. R., and Johnston, G. A. R.: Aminoacids transmitters in the mammalian central nervous system. Ergeb. Physiol. Biol. Chem. Exp. Pharmakol. **69:** 97–188, 1974.
80. Curtis, D. R., Duggan, A. W., Felix, D., Johnston, G. A. R., and McLennan, H.: Antagonism between bicuculline and GABA in the cat brain. Brain Res. **33:** 57–73, 1971.

81. Curtis, D. R., Duggan, A. W., and Johnston, G. A. R.: The specificity of strychnine as a glycine antagonist in the mammalian spinal cord. Exp. Brain Res. **12:** 547–565, 1971.
82. Curtis, D. R., Phillis, J. N., and Watkins, J. C.: The depression of spinal neurones by τ-amino-n-butyric acid and β-alanine. J. Physiol. (Lond.) **146:** 185–203, 1959.
83. Cushny, A. R.: On the pharmacology of the respiratory centre. J. Pharmacol. Exp. Ther. **4:** 363–398, 1913.
84. Dahlstrom, A., and Fuxe, K.: Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand. **62:** suppl. 232, 1–55, 1964.
85. Dahlstrom, A., and Fuxe, K.: Evidence for the existence of monoamine neurons in the central nervous system. Acta Physiol. Scand. **64:** Suppl. 247, 3–85, 1965.
86. Davi, M. J., Sankaran, K., Simons, K. J., Simons, R. E. R., Seshia, M. M., and Rigatto, H.: Physiological changes induced by theophylline in the treatment of apnea of preterm infants. J. Pediatr. **92:** 91–95, 1978.
87. Davies, J., and Watkins, J. C.: The action of β-phenyl-GABA derivatives on neurons of the cat cerebral cortex. Brain Res. **70:** 501–505, 1974.
88. Davis, J. N., and Carlsson, A.: The effect of hypoxia on monoamine synthesis levels and metabolism in rat brain. J. Neurochem. **21:** 783–790, 1973.
89. Davis, J. N., Carlsson, A., MacMillan, V., and Siesjö, B. K.: Brain tryptophan hydroxylation: Dependence on arterial oxygen tension. Science **182:** 72–74, 1973.
90. Dayton, H. E., and Garrett, R. L.: Production of analgesia by cholinergic drugs. Proc. Soc. Exp. Biol. Med. **142:** 1011–1013, 1973.
91. DeMontigny, C., and Aghajanian, G. K.: Preferential action of 5-methoxytryptamine and 5-methoxydimethyltryptamine on presynaptic serotonin receptors: A comparative iontophoretic study with LSD and serotonin. Neuropharmacology **16:** 811–818, 1977.
92. Dempsey, J. A., and Forster, H. V.: Mediation of ventilatory adaptations. Physiol. Rev. **62:** 262–346, 1982.
93. Denavit-Saubie, M., and Champagnat, J.: The effect of some depressing amino acids on bulbar respiratory and non-respiratory neurons. Brain Res. **97:** 356–361, 1975.
94. Denavit-Saubie, M., and Champagnat, J.: Action of aminoacids on cat respiratory neurons. Collegium Internationale Neuro-psychopharmacologicum, Abstr. 105, Gothenberg, 1980.
95. Denavit-Saubie, M., Champagnat, J., and Surun, M. P.: Are aminoacid transmitters implicated in the central generation of the respiratory rhythm. An iontophoretic study of medullary neurons. Neurosci. Abstr. **11:** 943, 1981.
96. Denavit-Saubie, M., Champagnat, J., and Zieglgansberger, W.: Effects of opiates and methionine-enkephalin on pontine and bulbar respiratory neurons of the cat. Brain Res. **155:** 55–67, 1978.
97. Dhumal, V. R., Gulati, O. D., Raghunath, P. R., and Siviramakrsishna, N.: Analysis of the effects on body temperature of intracerebroventricular injection in anesthetized dogs of gamma-aminobutyric acid. Br. J. Pharmacol. **50:** 513–524, 1974.
98. Doherty, J. D., Hattox, S. E., Snead, O. C., and Roth, R. H.: Identification of endogenous τ-hydroxybutyrate in human and bovine brain and its regional distribution in human, guinea pig, and rhesus monkey brain. J. Pharmacol. Exp. Ther. **207:** 130–139, 1978.
99. Dratman, M. B., Goldman, M., Crutchfield, F. L., and Gordon, J. T.: Nervous system role of iodocompounds in blood pressure regulation. Life Sci. **30:** 611–619, 1982.
100. Elam, M., Tai, Y., Thoren, A., and Svensson, T. H.: Hypercapnia and anxiety: Increased activity in central and peripheral noradrenergic neurons. Collegium Internationale, Neuro-psychopharmacologicum, Abstr. 186, Gothenberg, 1980.
101. Elam, M., Yao, T., Thoren, P., and Svensson, T. H.: Hypercapnia and hypoxia: Chemoreceptor-mediated control of locus coeruleus neurons and splanchnic sympathetic nerves. Brain Res. **222:**373–381, 1981.
102. Elde, R., Hökfelt, T., Johansson, O., and Terenius, L.: Immunohistochemical studies using antibodies to leucine-enkephalin: Initial observations on the nervous system of the rat. Neuroscience **1:** 349–351, 1976.
103. Eldridge, F. L., and Millhorn, D. E.: Central regulation of respiration by endogenous neurotransmitters and neuromodulators. Annu. Rev. Physiol. **43:** 121–135, 1981.
104. Eldridge, F. L., Millhorn, D. E., and Waldrop, T. G.: Exercise hyperpnea and locomotion: Parallel activation from the hypothalamus. Science **211:** 844–846, 1981.
105. Eldridge, F. L., Millhorn, D. E., and Waldrop, T. G.: Mechanism of hyperpnea induced by aminophylline. Physiologist **24:** 102, 1981.
106. Eldridge, F. L., Millhorn, D. E., and Waldrop, T. G.: Adenosine receptors and the methylxanthenes. Fed. Proc. **41:** 1690, 1982.
107. Elliott, K. A. C., and Hobbiger, F.: Gamma-aminobutyric acid: Circulatory and respiratory effects in different species; Reinvestigation of the anti-strychnine action in mice. J. Physiol. (Lond.) **146:** 70–84, 1959.
108. Emerson, C. H., Frohman, L. A., Szabo, M., and Thakkar, I.: TRH immunoreactivity in human urine. Evidence for dissociation from TRH. J. Clin. Endocrinol. Metab. **45:** 392–399, 1977.
109. Emson, P. C.: Peptides as neurotransmitter candidates in the mammalian CNS. Prog. Neurobiol. **13:** 61–116, 1979.
110. Engberg, G., Svensson, T. H., Rosell, S., and Folkers, K.: A synthetic peptide as an antagonist of substance P. Nature (Lond.) **293:** 222–223, 1981.
111. Engle, L. A., and Ritchie, B.: Ventilatory response to inhaled carbon dioxide in hyperthyroidism. J. Appl. Physiol. **30:** 173–177, 1971.
112. Enna, S. J., and Maggi, A.: Minireview. Biochemical Pharmacology of gabaergic agonists. Life Sci. **24:** 1727–1738, 1979.
113. Fahn, S.: Regional distribution studies of GABA and other putative neurotransmitters and their enzymes. *In* GABA in Nervous System Function, ed. by E. Roberts, T. N. Chase, and D. B. Tower, pp. 169–186, Raven Press, New York, 1976.
114. Fallert, M., Bohmer, G., Dinse, H. R. D., Sommer, T. J., and Bittner, A.: Microelectrophoretic application of putative neurotransmitters onto various types of bulbar respiratory neurons. Arch. Ital. Biol. **117:** 1–11, 1979.
115. Farber, J. P., Connors, A. F., Gisolfi, C. V., McCaffree, D. R., and Smith, R. M.: Effects on breathing of putative neurotransmitters in the rostral hypothalamus of the rat. Brain Res. Bull. **6:** 13–17, 1981.
116. Farber, J. P., and Maltby, M. A.: Effects of apomorphine on control of breathing in rats. Neuropharmacology **19:** 63–68, 1980.
117. Feldman, J. L.: Interactions between brainstem respiratory neurons. Fed. Proc. **40:** 2384–2388, 1981.
118. Feldman, J. L., Cohen, M. I., and Wolotsky, P.: Powerful inhibition of pontine respiratory neurons by pulmonary afferent activity. Brain Res. **104:** 341–346, 1976.
119. Fleetham, J. A., Clarke, H., Dhingra, S., Chernick, V., and Anthonisen, N. R.: Endogenous opiates and chemical control of breathing in humans. Am. Rev. Respir. Dis. **121:** 1045–1049, 1980.
120. Florez, J., and Borison, H. L.: Effects of central depressant drugs on respiratory regulation in the decerebrate cat. *Respir. Physiol.* **6:** 318–329, 1969.
121. Florez, J., Delgado, G., and Armijo, J. A.: Adrenergic and serotonergic mechanisms in morphine-induced respiratory depression. Psychopharmacologia **24:** 258–274, 1972.
122. Florez, J., Mediavilla, A., and Pazos, A.: Respiratory effects of β-endorphin. D-ALA^2-met-enkephalinamide, and met-enkephalin injected into the lateral ventricle and the pontomedullary subarachnoid space. Brain Res. **199:** 197–206, 1980.
123. Folgering, H.: Central β-adrenergic effects on the control of ventilation in cats. Respiration **39:** 131–138, 1980.
124. Folgering, H., and Braakhekke, J.: Ventilatory response to hypercapnia in normal subjects after propranolol, metoprolol and oxprenolol. Respiration **39:** 139–143, 1980.
125. Folkers, K., Hörig, J., Rosell, S., and Björkroth, U.: Chemical design of antagonists of substance P. Acta Physiol. Scand. **111:** 505–506, 1981.
126. Fonnum, F., and Storm-Mathisen, J.: High affinity uptake of glutamate in terminals of corticostriatal axons. Nature (Lond.) **266:** 377–378, 1977.
127. Fukuda, Y., and Honda, Y.: pH-sensitive cells at ventrolateral surface of rat medulla oblongata. Nature (Lond.) **256:** 317–318, 1975.
128. Fuxe, K., Andersson, K., Ogren, S. O. Perez de la, Mora, M., Schwarcz, R., Hökfelt, T., Eneroth, P., Gustafsson, J. A., and Skett, P.: GABA neurons and their interaction with monoamine neurons. An anatomical, pharmacological and functional analysis. *In* GABA-Neurotransmitters, Pharmacochemical Biochemical and Pharmacological Aspects, ed. by P. Krogsgaard-Larsen, J. Scheel-Kruger, and H. Kofod, pp. 74–94, Munksgaard, Copenhagen, Academic Press, New York, 1979.
129. Gallager, D. W., Mallorga, P., Thomas, J. W., and Tallman, J. F.: GABA-benzodiazepine interactions: Physiological, pharmacological and developmental aspects. Fed. Proc. **39:** 3043–3049, 1980.
130. Gamse, R., Holzer, P., Lembeck, F.: Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br. J. Pharmacol. **68:** 207–213, 1980.
131. Gamse, R., Leeman, S. E., Holzer, P., and Lembeck, F.: Effect of capsaicin on the content of somatostatin, substance P and neurotensin in the control and peripheral nervous system of the rats. *In* Synaptic Constituents in Health and Disease, ed. by M. Brzin, D. Sket, and H. Bachelard, p. 275, Mladinska Knjiga-Pergamon Press, Ljubljana, Yugoslavia, 1980.
132. Garcia deYebenes Prous, J., Carlsson, A., and Mena Gomez, M. A.: The effect of CO_2 on monoamine metabolism in rat brain. Naunyn-Schmiedebergs Arch. Pharmakol. **301:** 11–15, 1977.
133. Gen, M. C., and Valdman, A. V.: Experimental observations of the pontine respiration center. Prog. Brain Res. **20:** 148–170, 1967.
134. Ghose, K., Holmes, K. M., and Matthewson, K.: Complications of baclofen overdosage. Postgrad. Med. J. **56:** 865–867, 1980.
135. Gillis, R. A., Helke, C. J., Hamilton, B. L., Norman, W. P., and Jacobowitz, D. M.: Evidence that substance P is a neurotransmitter of baro- and chemoreceptor afferents in nucleus tractus solitarius. Brain Res. **181:** 476–481, 1980.
136. Goldstein, A., Tachibana, S., Lowney, L. I., Hunkapiller, M., and Hood, L.: Dynorphin (1–13), an extraordinarily potent opioid peptide. Proc. Natl. Acad. Sci. U.S.A. **76:** 6666–6670, 1979.
137. Goode, P. G., Rhodes, K. F., and Waterfall, J. F.: The analgesia and respiratory effects of meptazinol, morphine, and pentazocine in the rat. J. Pharm. Pharmacol. **31:** 793–795, 1979.

138. GRABOWSKA, M.: Influence of midbrain raphe lesion on some pharmacological and biochemical effects of apomorphine in rats. Psychopharmacologia **39:** 315–322, 1974.
139. GRABOWSKA, M., PRZEWLOCKI, R., AND SMIALOWSKA, M.: On the direct influence of apomorphine on central serotonin neurons. J. Pharm. Pharmacol. **28:** 64–65, 1976.
140. GRANATA, A. R., AND WOODRUFF, G. N.: A central hypertensive action of substance P in rats. Int. Res. Commun. System Med. Sci. **8:** 205, 1980.
141. GREEN, A. R., AND GRAHAME-SMITH, D. G.: TRH potentiates behavioral changes following increased brain 5-hydroxytryptamine accumulation in rats. Nature (Lond.) **251:** 524–526, 1974.
142. GRUNSTEIN, M. M., HAZINSKI, T. A., AND SCHLUETER, M. A.: Respiratory control during hypoxia in newborn rabbits: Implied action of endorphins. J. Appl. Physiol., **51:** 122–130, 1981.
143. GRUNSTEIN, M. M., YOUNGES, M., AND MILIC-EMILI, J.: Control of tidal volume and respiratory frequency in anesthetized cats. J. Appl. Physiol. **35:** 463–476, 1973.
144. HAEUSLER, G., AND OSTERWALDER, R.: Evidence suggesting a transmitter or neuromodulatory role for substance P at the first synapse of the baroreceptor reflex. Naunyn-Schmiedebergs Arch. Pharmacol. **314:** 111–121, 1980.
145. HEDNER, J., HEDNER, T., BERGMAN, B., IVERSEN, K., AND JONASON, J.: Effects of GABA and some GABA analogues on respiratory regulation in the preterm rabbit. Biol. Neonate, in press, 1982.
146. HEDNER, J., HEDNER, T., BERGMAN, B., AND LUNDBERG, D.: Respiratory depression of GABA-ergic drugs in the preterm rabbit. J. Dev. Physiol. **2:** 401–407, 1980.
147. HEDNER, J., HEDNER, T., JONASON, J., AND LUNDBERG, D.: Central respiratory stimulant effect by thyrotropin releasing hormone in the rat. Neurosci. Lett. **25:** 317–320, 1981.
148. HEDNER, J., HEDNER, T., JONASON, J., AND LUNDBERG, D.: GABA-ergic mechanisms in central respiratory control in the anesthetized rat. Naunynn-Schmiedebergs Arch. Pharmakol. **317:** 315–320, 1981.
149. HEDNER, J., HEDNER, T., JONASON, J., AND LUNDBERG, D.: Evidence for a dopamine interaction with the central respiratory control system in the rat. Eur. J. Pharmacol., **81:** 603–615, 1982.
150. HEDNER, J., HEDNER, T., WESSBERG, P., AND JONASON, J.: Respiratory effects of some putative neurotransmitter amino acids. Naunyn-Schmiedebergs Arch. Pharmakol., in press, 1982.
151. HEDNER, J., JONASON, J., AND LUNDBERG, D.: Respiratory effects of gamma-hydroxybutyric acid in anesthetized rats. Neural Transmission **49:** 179–186, 1980.
152. HEDNER, T., HEDNER, J., JONASON, J., AND LUNDBERG, D.: Evidence suggesting a role for substance P in central respiratory regulation in the rat. Acta. Physiol. Scand. **112:** 487–489, 1981.
153. HEDNER, T., HEDNER, J., BERGMAN, B., JONASON, J., AND LUNDBERG, D.: Transient apnea after an enkephalin analogue in the preterm rabbit. Biol. Neonate **39:** 290–294, 1981.
154. HEDNER, T., HEDNER, J., JONASON, J., AND LUNDBERG, D.: Respiratory effects of TRH in preterm rabbits. Pediatr. Res. **16:** 543–548, 1982.
155. HEDNER, T., AND LUNDBORG, P.: GABA levels and turnover in neonatal rat brain during asphyxia and recovery. Acta Physiol. Scand, in press, 1982.
156. HEISTAD, D. D., WHEELER, R. C., MARK, A. L., SCHMID, P. G., AND ABBOUD, M.: Effects of adrenergic stimulation on ventilation in man. J. Clin. Invest. **51:** 1469–1475, 1972.
157. HELKE, C. J., O'DONAHUE, T. L., AND JACOBOWITZ, D. M.: Substance P as a baro- and chemo-receptor afferent neurotransmitter: Immunocytochemical and neurochemical evidence in the rat. Pepetides **1:** 1–9, 1980.
158. HEMANS, C., AND NEIL, E.: Reflexogenic Area of the Cardiovascular System. Churchill, London, 1958.
159. HIRSH, K., AND WANG, S. L.: Respiratory stimulant effects of ethamivan and picrotoxin. J. Pharmacol. Exp. Ther. **193:** 657–663, 1975.
160. HJORTH, J., CARLSSON, A., WIKSTROM, H., LINDBERG, P., SANCHEZ, D., HACKSELL, U., AVIDSSON, L. E., SVENSSON, U., AND NILSSON, J. L. G.: 3-PPP, A new centrally acting DA-receptor agonist with selectivity for autoreceptors. Life Sci. **28:** 1225–1238, 1981.
161. HÖKFELT, T., ELDE, R., JOHANSSON, O., LJUNGDAHL, Å., SCHULTZBERG, M., FUXE, K., GOLDSTEIN, M., NILSSON, G., PERNOW, B., TERENIUS, L., GANTEN, D., JEFFCOATE, S. L., REHFELD, J., AND SAID, S.: Distribution of peptide containing neurones. *In* Psychopharmacology: A Generation of Progress, ed. by M. A. Lipton, A. Dimascio, and K. F. Killam, pp. 39–66, Raven Press, New York, 1978.
162. HÖKFELT, T., ELDE, R., JOHANSSON, O., TERENIUS, L., AND STEIN, L.: The distribution of enkephalin immunoreactive cell bodies in the rat central nervous system. Neurosci. Lett. **5:** 25–31, 1977.
163. HÖKFELT, T., FUXE, K., GOLDSTEIN, M., AND JOHANSSON, O.: Evidence for adrenergic neurons in the rat brain. Acta Physiol. Scand. **89:** 286–288, 1973.
164. HÖKFELT, T., FUXE, K., GOLDSTEIN, M., AND JOHANSSON, O.: Immunohistochemical evidence of adrenaline neurons in the rat brain. Brain Res. **66:** 235–251, 1974.
165. HÖKFELT, T., FUXE, K., JOHANSSON, O., JEFFCOATE, S., AND WHITE, N.: Thyrotropin releasing hormone (TRH)-containing nerve terminals in certain brain stem nuclei and in the spinal cord. Neurosci. Lett. **1:** 133–139, 1975.
166. HÖKFELT, T., JOHANSSON, O., LJUNGDAHL, Å., LUNDBERG, J. M., AND SCHULTZBERG, M.: Peptidergic neurones. Nature (Lond.) **284:** 515–521, 1980.
167. HOLADAY, J. W., AND FADEN, A. I.: Naloxone acts at central opiate receptors to reverse hypotension, hypothermia, and hypoventilation in spinal shock. Brain Res. **189:** 295–299, 1980.
168. HOLZER, P., AND HAGMÜLLER, K.: On the site of action of intravascular GABA on respiration of the rat. Zool. Jahrb. Abt. Allg. Zool Physiol. Tiere **82:** 505–514, 1978.
169. HOLZER, P., AND HAGMÜLLER, K.: Transient apnea after systemic injection of GABA in the rat. Naunyn-Schmiedebergs Arch. Pharmakol. **308:** 55–60, 1979.
170. HORITA, A., CARINO, M. A., AND CHESNUT, R. M.: Influence of thyrotropin-releasing hormone (TRH) on drug-induced narcosis and hypothermia in rabbits. Psychopharmacol. Bull. **49:** 57–62, 1976.
171. HORST, W. D., AND SPIRT N.: A possible mechanism for the anti-depressant activity of thyrotropin releasing hormone. Life Sci. **15:** 1073–1082, 1974.
172. HÖSLI, L., TEBECIS, A. K., AND FILIAS, N.: Effects of glycine, β-alanine and GABA and their interaction with strychnine, on brain stem neurones. Brain Res. **16:** 293–295, 1969.
173. HOWARD, J. L., AND BREESE, G. R.: Physiological and behavioral effects of centrally administered 6-hydroxydopamine in cats. Pharmacol. Biochem. Behav. **2:** 651–661, 1974.
174. HOWE, P. R. C., COSTA, M., FURNESS, J. B., AND CHALMERS, J. P.: Simultaneous demonstration of phenylethanolamine N-methyl-transferase immunofluorescent and catecholamine fluorescent nerve cell bodies in the rat medulla oblongata. Neuroscience **5:** 2229–2238, 1980.
175. HRUSKA, R. E., THUT, P. D., HUXTABLE, R., AND BRESSLER, R.: Hypothermia produced by taurine. *In* Taurine, ed. by R. Huxtable and A. Barbeau, pp. 347–356, Raven Press, New York, 1976.
176. HURLÉ, M. A., MEDIAVILLA, A., AND FLÓREZ, J.: Morphine, pentobarbital and naloxone in the ventral medullary chemosensitive areas: Differential respiratory and cardiovascular effects. J. Pharmacol. Exp. Ther. **220:** 642–647, 1982.
177. JACKSON, I. V., VOLAVKA, J., JAMES, B., AND REKER, D.: The respiratory components of tardive dyskinesia. Biol. Psychiatry **15:** 485–487, 1980.
178. JESSEL, T. M., AND IVERSEN, L. L.: Opiate analgetics inhibit substance P release from rat trigeminal nucleus. Nature (Lond.) **268:** 549–551, 1977.
179. JOHNSON, J. L.: Glutamic acid as a synaptic transmitter in the nervous system. A review. Brain Res. **37:** 1–19, 1972.
180. JOHNSTON, G. A. R., ALLAN, R. D., KENNEDY, S. M. E., AND TWITCHIN, B.: Systematic study of GABA analogues of restricted conformation. *In* GABA Neurotransmitters, ed. by P. Krogsgaard-Larsen, J. Scheel-Druger, and H. Kofod, pp. 149–164, Munksgaard, Copenhagen, 1979.
181. JOORABCHI, B.: Expressions of the hyperventilation syndrome in childhood. Clin. Pediatr. **16:** 1110–1115, 1977.
182. KAGAWA, S., STAFFORD, M. J., WAGGENER, T. H., AND SEVERINGHAUS, J. W.: No effect of naloxone on hypoxia-induced ventilatory depression in adults. J. Appl. Physiol. **52:**1030–1034, 1982.
183. KALIVAS, P. W. AND HORITA, A.: Thyrotropin-releasing hormone: central site of action in antagonism of pentobarbital narcosis. Nature (Lond.) **278:** 461–463, 1979.
184. KALLOS, T., AND CARUSO, F. S.: Respiratory effects of butorphanol and pethidine. Anesthesia **34:** 633–637, 1979.
185. KEANE, P. E., DEGEURCE, A.,RENAUD, B., CRESPI, F., AND PUJOL, J. R.: Alteration of tyrosine hydroxylase and dopamine-β-hydroxylase activity in the locus coeruleus after 5,6-dihydroxytryptamine. Neurosci. Lett. **8:** 119–150, 1978.
186. KELLER, H. H., BARTHOLINI, G., AND PLETSCHER, A.: Enhancement of cerebral noradrenaline turnover by thyrotropin-releasing hormone. Nature (Lond.) **248:** 528–529, 1974.
187. KELLOKUMPU. S., VUOLTEENAHO, J., AND LEPPALUOTO, J.: Behavior of rat hypothalamic and extrahypothalamic immunoreactive TRF in thin-layer chromatography and high pressure liquid chromatography (HPLC). Life Sci. **26:** 475–480, 1980.
188. KELTZ, H., SAMORTIN, T., AND STONE, D. J.: Hyperventilation: A manifestation of exogenous beta-adrenergic stimulation. Am. Rev. Respir. Dis. **105:** 637–640, 1972.
189. KIRSTEN, E. B., SATAYAVIVAD, J., ST. JOHN, W. M., AND WANG, S. C.: Alteration of medullary respiratory unit discharge by iontophoretic application of putative neurotransmitters. Br. J. Pharmacol. **63:** 275–281, 1978.
190. KLIEGMAN, R., AND FANAROFF, A. A.: Caution in use of dopamine in the neonate. J. Pediatr. **93:** 540–541, 1978.
191. KNILL, R. L., CLEMENT, J. L., AND THOMPSON, W. R.: Epidural morphine causes delayed and prolonged ventilatory depression. Can. Anaesth. Soc. J. **28:** 537–543, 1981.
192. KOBAYASI, S., AND MURATA, K.: Phrenic activity during severe hypercapnia in vagotomized rabbits. J. Appl. Physiol. **47:** 91–97, 1979.
193. KOSTOWSKI, W., SAMANIN, R., BAREGGI, S. R., MARE, V., GARRATTIN, S., AND VALZELLI, L.: Biochemical aspects of the interactions between midbrain raphe and locus coeruleus in the rat. Brain Res. **82:** 178–182, 1974.
194. KRAEMER, G. W., MUELLER, R. A., BREESE, G. R., PRANGE, A. J., LEWIS, J. K., MORRISON, H., AND MCKINNEY, W. T.: Thyrotropin releasing hormone: Antagonism of pentobarbital narcosis in the monkey. Pharmacol. Biochem. Behav. **4:** 709–712, 1976.
195. KRIEGER, A. J., CHRISTENSEN, H. D., AND SAPRU, H. N.: Changes in

ventilatory patterns after ablation of various respiratory feedback mechanisms. J. Appl. Physiol. **33:** 431–435, 1972.
196. KROGSGAARD-LARSEN, P., HONORE, T., AND THYSSEN, K.: GABA receptor agonists: Design and structure activity studies. *In* GABA Neurotransmitter, ed. by P. Krogsgaard-Larsen, J. Scheel-Druger, and H. Kofod, pp. 201–216, Munksgaard, Copenhagen, 1979.
197. LACKNER, K. J.: Mapping of monoamine neurones and fibers in the cat lower brainstem and spinal cord. Anat. Embryol. **161:** 169–195. 1980.
198. LALLEY, P. M.: Inhibition of phrenic and sympathetic vasomotor neurons in cats by serotonin analogue 5-methoxy-N,N-dimethyltryptamine. J. Pharmacol. Exp. Ther. **220:** 39–48, 1982.
199. LAMBERT, G. A., FRIEDMAN, E., BUCHWEITZ, E., AND GERSHON, S.: Involvement of 5-hydroxytryptamine in the central control of respiration, blood pressure and heart rate in the anesthetized rat. Neuropharmacology **17:** 807–813, 1978.
200. LAWSON, E. E., WALDROP, T. G., AND ELDRIDGE, F. L.: Naloxone enhances respiratory output in cats. J. Appl. Physiol.: Respir. Environ. Exerc. Physiol. **47:** 1105–1111, 1979.
201. LEE, J. C., AND DOWNING, S. E.: Laryngeal reflex inhibition of breathing in piglets: Influence of anemia and catecholamine depletion. Am. J. Physiol. **239:** R25–R30, 1980.
202. LEGER, L., DEGUEURCE, A. M., AND PUJOL, J. F.: Origine de l'innervation serotoninergique du locus coeruleus chez le rat. C.R. Acad. Sci. Paris **290:** 807–810, 1980.
203. LEMBECK, F.: Zur Frage der zentralen Übertragung affenter impulse III. Das Vorkommen and die Bedeutung der Substanz P in der dorsalen Wurzeln des Ruckermarks. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. **219:** 197–213, 1953.
204. LI, C. H., AND CHUNG, D.: Isolation and structure of an untriakontapeptide with opiate activity from camel pituitary glands. Proc. Natl. Acad. Sci. U.S.A. **73;** 1145–1148, 1976.
205. LUNDBERG, D., BREESE, G. R., AND MUELLER, R. A.: Dopaminergic interaction with the respiratory control system in the rat. Eur. J. Pharmacol. **54:** 153–159, 1979.
206. LUNDBERG, D. B., BREESE, G. R., AND MUELLER, R. A.: Aminophylline may stimulate respiration in rats by activation of dopaminergic receptors. J. Pharmacol. Exp. Ther. **217:** 215–221, 1981.
207. LUNDBERG, D. B., MUELLER, R. A., AND BREESE, G. R.: Dopaminergic and serotonergic modulation of respiratory drive. *In* Catecholamines: Basic and Clinical Frontiers, ed. by E. Usdin, I. J. Kopin and J. Barchas, pp. 526–528, Pergamon Press, New York, 1979.
208. LUNDBERG, D., MUELLER, R. A., AND BREESE, G. R.: An evaluation of the mechanism by which serotonergic activation depresses respiration. J. Pharmacol. Exp. Ther. **212:** 397–404, 1980.
209. LUNDBERG, D., MUELLER, R. A., AND BREESE, G. R.: Effects of vagotomy and glossopharyngectomy on respiratory response to dopamine-agonists. Acta Physiol. Scand. **114:** 81–89, 1982.
210. MAJ, J., BARAN, L., MICHALUK, J., PALIDER, W., AND RAWLOW, A.: The central antiserotonin activity of neuroleptics. Pol. J. Pharmacol. Pharm. **30:** 407–409, 1978.
211. MAJ, J., KAPTURKIEWICZ, F., AND M. I. CHALUK, J.: Central action of nomifensin. Pol. J. Pharmacol. Pharm. **28:** 557–562, 1976.
212. MAJ, J., MOGILNICKA, E., AND KLIMEK, V.: Dopaminergic stimulation enhances the utilization of noradrenaline in the central nervous system. J. Pharm. Pharmacol. **29:** 569–570, 1977.
213. MALTHE-SÖRENSSEN, D., WOOD, P. L., CHENEY, D. L., AND COSTA, E.: Modulation of the turnover rate of acetylcholine in rat brain by intraventricular injections of thyrotropin releasing hormone, somatostatin, neurotensin and angiostensin II. J. Neurochem. **31:** 685–691, 1978.
214. MAMELAK, M., AND WEBSTER, P.: Treatment of narcolepsy and sleep apnea with gammahydroxybutyrate: A clinical and polysomnographic case study. Sleep **4:** 105–111, 1981.
215. MANGIN, P., KRIEGER, J., BORG, J., WARTER, J. M., AND KURTZ, D.: Biogenic amine metabolism in sleep apnea syndrome. Adv. Biosci. **21:** 217–219, 1979.
216. MARSHALL, E. K., JR., WALZL, E. M., AND LEMESSURIER, D. H.: Picrotoxin as a respiratory stimulant. J. Pharmacol. Exp. Ther. **60:** 472–486, 1937.
217. MARTIN, DEL RIO, R., ORENSANZ MUNOZ, L. M., AND DEFEUDIS, F. V.: Contents of β-alanine and T-amino-butyric acid in regions of rat CNS. Exp. Brain Res. **27:** 225–227, 1977.
218. MARTIN, W. E., EADES, C. G., THOMPSON, J. A., HUPPER, R. E., AND GILBERT, P. E.: The effects of morphine and nalorphine-like drugs in nondependent and morphine dependent chronic spinal dog. J. Pharmacol. Exp. Ther. **197:** 517–532, 1976.
219. MASSOTTI, M., AND LONGO, V. G.: α-Chloralose and the central dopaminergic system. J. Pharm. Pharmacol. **30:** 667, 1978.
220. MCCARTY, R., CHIUEH, C. C., AND KOPIN, I. J.: Differential behavioral responses of spontaneously hypertensive (SHR) and normotensive (WKY) rats to amphetamine. Pharmacol. Biochem. Behav. **12:** 53–59, 1980.
221. MCCLOSKEY, D. I., AND MITCHELL, J. H.: Reflex cardiovascular and respiratory responses originating in exercising muscle. J. Physiol. (Lond.) **224:** 173–186, 1972.
222. MCCRIMMON, D. R., AND LALLEY, P. M.: Inhibition of respiratory neural discharge in cats by clonidine and 5-hydroxytryptophan. Fed. Proc. **39:** 952, 1980.
223. MCGILLIARD, K. L., AND TAKEMORI, A. E.: The effect of dopaminergic modifiers on morphine-induced analgesia and respiratory depression. Eur. J. Pharmacol. **54:** 61–68, 1979.
224. MEDIAVILLA, A., FERIA, M., FERNANDEX, J. F., CAGIGAS, P., PAZOS, A., AND FLOREZ, J.: The Stimulatory action of *d*-amphetamine on the respiratory centre, and its mediation by a central α-adrenergic mechanism. Neuropharmacology **18:** 133–143, 1979.
225. MELDRUM, M. J., AND ISOM, G. E.: Role of monoaminergic systems in morphine-induced respiratory depression. Neuropharmacology **20:** 169–175, 1981.
226. MENA GOMEZ, M. A., CARLSSON, A., AND GARCIA DE YEBENES, J.: The effect of β-alanine on motor behaviour, body temperature and cerebral monoamine metabolism in rat. J. Neural Transmission **43:** 1–9, 1978.
227. MERRILL, E. G.: Finding a respiratory function for the medullary respiratory neurones. *In* Essays on the Nervous System. ed. by R. Bellairs and E. G. Gray, pp. 457–486, Clarendon Press, Oxford, 1974.
228. MESSING, R. B., AND LYTLE, L. D.: Serotonin-containing neurons: Their possible role in pain and analgesia. Pain **4:**1–21, 1977.
229. METCALF, G.: TRH: A possible mediator of thermoregulation. Nature (Lond.) **252:** 310–311, 1974.
230. METCALF, G., AND MYERS, R. D.: A comparison between the hypothermia induced by intraventricular injections of thyrotropin-releasing hormone, noradrenaline or calcium ions in unanesthetized cats. Br. J. Pharmacol. **58:** 489–495, 1976.
231. MILIC-EMILI, J.: Recent advances in the evaluation of respiratory drive. *In* Anesthesia and Respiratory Function, ed. by Enid R. Kafer, International Anesthesiology Clinics vol. 15, pp. 39–58, Little, Brown and Company, Boston, 1977.
232. MILLER, R. J.: Multiple opiate receptors for multiple opioid peptides. Med. Biol. **60:** 1–6, 1982.
233. MILLHORN, D. E., ELDRIDGE, F. L., AND WALDROP, T. G.: Prolonged stimulation of respiration by a new central neural mechanism. Respir. Physiol. **41:** 87–103, 1980.
234. MITCHELL, G. S., SMITH, C. A., JAMESON, L. C., VIDRUK, E. H., AND DEMPSEY, J. A.: Ventilatory control in goats following serotonin depletion with *p*-chlorophenylalanine (pCPA). Fed. Proc. **41:** 1690, 1982.
235. MITCHELL, R. A., AND HERBERT, D. A.: The effect of carbon dioxide on the membrane potential of medullary respiratory neurons. Brain Res. **75:** 345–349, 1974.
236. MITCHELL, R. A., LOESCHCKE, H. H., MASION, W. H., AND SEVERINGHAUS, J. W.: Respiratory responses mediated through superficial chemosensitive areas on the medulla. J. Appl. Physiol. **18:** 523–533, 1963.
237. MOGILNICKA, E., SCHEEL-KRUGER, J., KLIMEK, V., AND GOLEMBIOWSKAN NIKITIN, K.: The influence of antiserotonergic agents on the action of dopaminergic drugs. Br. J. Pharmacol. Pharm. **29:** 31–38, 1977.
238. MOORE, R. Y., AND BLOOM, F. E.: Central catecholamine neuron systems: Anatomy and physiology of the dopamine system. Ann. Rev. Neurosci. **1:** 129–169, 1978.
239. MOSS, I. R., AND FRIEDMANN, E.: β-Endorphin effects on respiratory regulation. Life Sci. **23:** 1271–1276, 1978.
240. MUELLER, R. A., BREESE, G. R., AND KILTS, C. D.: Stimulation of respiration by thyrotropin-releasing hormone. Pharmacologist **23:** 139, 1981.
241. MUELLER, R. A., LUNDBERG, D., AND BREESE, G. R.: Evidence that respiratory depression by serotonin agonists may be exerted in the central nervous system. Pharmacol. Biochem. Behav. **13:** 247–255, 1980.
242. MUELLER, R. A., LUNDBERG, D. B., AND BREESE, G. R.: Alteration of aminophylline-induced respiratory stimulation by perturbation of biogenic amine systems. J. Pharmacol. Exp. Ther. **218:** 593–599, 1981.
243. MUELLER, R. A., THOENEN, H., AND AXELROD, J.: Compensatory increase in adrenal tyrosine hydroxylase activity after chemical sympathectomy. Science **163:** 468–469, 1969.
244. MUELLER, R. A., WIDERLÖV, E., AND BREESE, G. R.: Effect of 2-chloradenosine on respiratory activity. Fed. Proc. **41:** 1725, 1982.
245. MUELLER, R. A., WIDERLÖV, E., AND BREESE, G. R.: Antagonism of 2-chloradenosine-induced respiratory depression by aminophylline and naloxone. Anesthesiology, **57:** A494, 1982.
246. MUSTAFA, M. E. K. Y., AND PURVES, M. J.: The effect of CO_2 upon discharge from slowly adapting stretch receptors in the lungs of rabbits. Respir. Physiol. **16:** 197–212, 1972.
247. MUSTCHIN, P., GRIBBIN, H. R., TATTERSFIELD, A. E., AND GEORGE, C. F.: Reduced respiratory responses to carbon dioxide after propranolol: A central action. Br. Med. J. **2:** 1229–1231, 1976.
248. NAGAI, Y., NARUMI, S., NAGAWA, Y., SAKURADA, O., UENO, H., AND ISHII, S.: Effect of thyrotropin-releasing hormone (TRH) on local cerebral glucose utilization by the autoradiographic 2-deoxy[^{14}C]glucose method, in conscious and pentobarbitalized rats. J. Neurochem. **35:** 963–971, 1980.
249. NAKATA, Y., KUSAKA, Y., SEGAWA, T., YAJIMA, H., AND KITAGAWA, K.: Substance P: Regional distribution and specific binding to synaptic membranes in rabbit central nervous system. Life Sci. **22:** 259–267, 1978.
250. NGAI, S.: Effects of morphine and meperidine on the central respiratory mechanisms in the cat; the action of levallorphan in antagonizing these effects. J. Pharmacol. Exp. Ther. **131:** 91–99, 1961.
251. NICOLL, R. A., SCHENKER, C., AND LEEMAN, S. E.: Substance P as a transmitter candidate. Annu. Rev. Neurosci. **3:** 227–268, 1980.
252. NIECHAJ, A.: Further studies on the slow rhythm of pulmonary respiration in the frog. Folia Biol. (Krakow) **17:** 49–62, 1960.
253. NIECHAJ, A.: The effect of catecholamines on the slow rhythm of pulmonary

respiration in the frog. Folia Biol. (Krakow) **19:** 371–384, 1971.
254. NIECHAJ, A.: The effect of cerebellectomy on the slow rhythm of pulmonary respiration in the frog. Folia Biol. (Krakow) **24:** 321–332, 1976.
255. NIEOULLON, A., CHERAMY, A., AND GLOWINSKI, J.: An adaptation of the push pull cannula method to study the *in vivo* release of [^{3}H]dopamine synthesized from [^{3}H]tyrosine in the cat caudate-nucleus: Effects of various physical and pharmacological treatments. J. Neurochem. **28:** 819–828, 1977.
256. NIEOULLON, A., CHERAMY, A., AND GLOWINSKI, J.: Control of the activity of the two dopaminergic systems by cortical, cerebellar, and sensory afferents in the cat. Appl. Neurophysiol. **42:** 51–53, 1979.
257. NIEOULLON, A., AND DUSTICIER, N.: Effects of α-chloralose on the activity of the nigrostriatal dopaminergic system in the cat. Eur. J. Pharmacol. **65:** 403–410, 1980.
258. OKTAY, J. S., ONUR, R., ILHAN, M., AND TÜRKER, R. K.: Potentiation of the morphine-induced respiratory rate depression by captopril. Eur. J. Pharmacol. **26:** 257–262, 1981.
259. OLIVER, C., ESKAY, R. L., BEN-JOHNATHAN, N., AND PORTER, J. C.: Distribution and concentration of TRH in the rat brain. Endocrinology **96:** 540–546, 1974.
260. OLNEY, J. W., RHEE, V., AND HO, O. L.: Kainic acid: A powerful neurotoxic analogue of glutamate. Brain Res. **77:** 507–512, 1974.
261. OLSEN, G. D., AND LEES, M. H.: Ventilatory response to carbon dioxide of infants following chronic prenatal methadone exposure. J. Pediatr. **96:** 983–989, 1980.
262. OLSON, E. B., JR., DEMPSEY, A. J., AND MCCRIMMON, D. R.: Serotonin and the control of ventilation in awake rats. J. Clin. Invest. **64:** 689–693, 1979.
263. OLSON, R. J., BROMBERG, B. B., AND ZIMMERMAN, T. J.: Apneic spells associated with timolol therapy in a neonate. Am. J. Ophthalmol. **88:** 120–122, 1979.
264. OREM, J.: Medullary respiratory neuron activity: Relationship to tonic and phasic REM sleep. J. Appl. Physiol. **48:** 54–65, 1980.
265. PADRON, F.: Effectos respiratorios y circulatorios de los estimulantes dopaminerguas y bromocriptina, y de su interaccion cen el haloperidol. Tesina de licencia tura, University de la Laguau, 1978.
266. PADRON, F., AND FLOREZ, J.: Blockade by intraventricular phentolamine of the respiratory and cardiovascular effects of bromocriptine. Arch. Farmacol. Toxicol. **4:** 211–220, 1978.
267. PAINTAL, A. S.: Vagal afferent fibres. Ergeb. Physiol. **52:** 74–156, 1963.
268. PALKOVITS, M., BROWNSTEIN, M., AND SAAVEDRA, J. M.: Serotonin content of the brain stem nuclei of the rat. Brain Res. **80:** 237–249, 1974.
269. PARIZEK, J., HASSLER, R., AND BAK, I. J.: Light and Electron microscopic autoradiography of substantia nigra of rat after intraventricular administration of tritum labelled norepinephrine, dopamine, serotonin. Z. Zellforsch. Mikrosk. Anat. **115:** 137–148, 1971.
270. PATRICK, J. M., AND PEARSON, S. B.: Propranolol and the ventilatory response to CO_2 and hypoxia in man. J. Physiol. (Lond.) **276:** 68–69P, 1978.
271. PEPPER, C. M. AND HENDERSON, G.: Opiates and opioid peptides hyperpolarize locus coeruleus neurons in vitro. Science **209:** 394–396, 1980.
272. PERRY, T. L., HANSEN, S., BERRY, K., MOK, C., AND LESK, D.: Free amino acids and related compounds in biopsies of human brain. J. Neurochem. **18:** 521–528, 1971.
273. PERSSON, B.: GABA-ergic Mechanisms in Blood Pressure Control. Thesis. Gotab, Küngalv, Sweden, 1980.
274. PERSSON, T., AND WALDECK, B.: Further studies on the possible interaction between dopamine and noradrenaline containing neurons in the brain. Eur. J. Pharmacol. **11:** 315–320, 1970.
275. PLOTNIKOFF, N. P., PRANGE, A. J., BREESE, G. R., AND ANDERSON, M. S.: Enhancement of DOPA activity by a hypothalamic hormone, thyrotropin releasing hormone, TRH. Science **178:** 417–418, 1972.
276. POIRIER, L. J., AND SOURKES, T. L.: Influence of the substantia nigra on the catecholamine content of the striatum. Brain **88:** 181–192, 1965.
277. POITRAS, D., AND PARENT, A.: Atlas of the distribution of monoamine containing nerve cell bodies in the brain stem of the cat. J. Comp. Neurol. **179:** 699–717, 1978.
278. POKORSKI, M., GRIEB, P., AND WIDEMAN, J.: Opiate system influences central respiratory chemosensors. Brain Res. **211:** 221–226, 1981.
279. PORSZASZ, J., SUCH, G. Y., AND PORSZASZ-GIBISZER, K.: Circulatory and respiratory chemo-reflexes. 1. Analysis of the site of action and receptor types of capsaicine. Acta Physiol. Acad. Sci. Hung. **12:** 189–205, 1957.
280. POST, R. N., KOTIN, J., GOODWIN, F. K., AND GORDON, E. K.: Psychomotor activity and cerebrospinal fluid amine metabolites in affective illness. Am. J. Psychiatry **130:** 67–72, 1973.
281. PRANGE, A. J., BREESE, G. R., WILSON, I. C., AND LIPTON, M. A.: Brain behavioral effects of hypothalamic releasing hormones: A generic hypothesis. *In* Anatomical Neuroendocrinology, ed by W. E. Stumpf and L. D. Grant, pp. 357–366. Karger, Basel, 1976.
282. PRANGE, A. J., NEMEROFF, C. B., LIPTON, M. A., BREESE, G. R., WILSON, I. C.: Peptides and the central nervous system. *In* Handbook of Psychopharmacology, ed. by L. L. Iverson, pp. 1–107, Plenum Press, New York, 1978.
283. PROUDFIT, H. K., AND ANDERSON, E. G.: Influence of serotonin antagonists on bulbospinal systems. Brain Res. **61:** 331–341, 1973.
284. PUJOL, J. F., STEIN, P., BLONDAUX, C., PETITEAN, F., FROMENT, J. L., AND JOUVET, M.: Biochemical evidence for interaction phenomena between noradrenergic and serotoninergic systems in the cat brain. *In* Frontiers in Catecholamine Research, ed. by E. Usdin and S. H. Snyder, pp. 771–772, Pergamon Press, 1973.
285. PURPURA, D. P., GIRADO, M., SMITH, T. G., AND GOMEZ, J. A.: Synaptic effects of systemic T-aminobutyric acid in cortical regions of increased vascular permeability. Proc. Exp. Biol. Med. **97:** 348–353, 1958.
286. REDMOND, D. E., JR.: Alterations in the function of the nucleus locus coeruleus: A possible model for studies of anxiety. *In* Animal Models in Psychiatry and Neurology, ed. by I. Hanin and E. Usdin, pp. 293–305, Pergamon Press, Oxford, New York, 1977.
287. REIS, D. J., TALMAN, T., PERRONE, M., DOBA, N., AND KUMADA, M.: *In* Baroreceptors and Hypertension, ed. by P. Sleight, Oxford Univ. Press, Oxford, 1980.
288. REMMERS, J. E., AND TSIATAS, W. G.: Effect of lateral cervical cord lesions on the respiratory rhythm of anesthetized, decerebrate cats after vagotomy. J. Physiol. (Lond.) **233:** 63–74, 1973.
289. RICHTER, D. W., CAMERER, H., MEESMANN, M., AND ROHRIG, N.: Studies on the synaptic interconnections between bulbar respiratory neurones of cats. Pflüger's Arch. Eur. J. Physiol. **380:** 245–257, 1979.
290. ROBERTS, E.: New directions in GABA research. I: Immunocytochemical studies of GABA neurons. *In* GABA-Neurotransmitters: Pharmacochemical, Biochemical and Pharmacological Aspects, ed. by P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod, pp. 28–45, Munksgaard, Copenhagen, 1979.
291. ROIZEN, M. F., AND JACOBOWITZ, D. M.: Studies on the origin of innervation of the noradrenergic area bordering on the nucleus raphe dorsalis. Brain Res. **101:** 561–568, 1976.
292. ROSELL, S., OLGART, L., GAZELIUS, B., PANOPOULUS, P., FOLKERS, K., AND HÖRIG, J.: Inhibition of antidromic and substance P induced vasodilation by a substance P antagonist. Acta Physiol. Scand. **111:** 381–382, 1981.
293. ROTH, R. H., WALTERS, J. R., AND AGHAJANIAN, G. K.: Effects of impulse flow on the release and synthesis of dopamine in the rat striatum. *In* Frontiers in Catecholamine Research, ed. by S. H. Snyder and E. Usdin, pp. 567–574, Pergamon Press, New York, 1973.
294. SAITO, K., KONISHI, S., AND OTSUKA, M.: Antagonism between Lioresal and substance P in rat spinal cord. Brain Res. **97:** 177–180, 1975.
295. SALMOIRAGHI, G. C., AND BURNS, B. D.: Localization and patterns of discharge of respiratory neurons in brain stem of cat. J. Neurophysol. **23:** 2–13, 1960.
296. SAMANIN, R., AND GARATTINI, S.: The serotonergic system in the brain and its possible functional connections with other aminergic systems. Life Sci. **17:** 1201–1210, 1975.
297. SAMII, K., FERET, J., HARARI, A., AND VIARS, P.: Selective spinal analgesia. Lancet **1:** 1142, 1979.
298. SAMPSON, S. R.: Mechanism of efferent inhibition of carotid body chemoreceptors in the cat. Brain Res. **45:** 266–270, 1972.
299. SANTIAGO, T. V., REMOLINA, C., SCOLES, V., III, AND EDELMAN, N. H.: Endorphins and the control of breathing: Ability of naloxone to restore flow-resistive load compensation in chronic obstructive pulmonary disease. N. Engl. J. Med. **304:** 1190–1195, 1981.
300. SCHAEFER, K. E.: Respiratory pattern and respiratory response to CO_2. J. Appl. Physiol. **13:** 1–14, 1958.
301. SCHEEN, A., JUCHMES, J., ET CESSION-FOSSION, A.: Dimunution de l 'hy'perventilation d'exercise par le blocage des recepteurs beta-adrenergigues. C.R. Soc. Biol. **170:** 220–223, 1976.
302. SCHLAFKE, M. E.: Central chemosensitivity: Neurophysiology and contribution to regulation. *In* Acid Base Homeostasis of the Brain Extracellular Fluid and the Respiratory Control System, ed. by H. H. Loeschcke, pp. 66–80, Publishing Sciences Group, Inc., Littleton, MA, 1975.
303. SCHLAFKE, M., AND LOESCHCKE, H. H.: Lokalisation eines an der Regulation von Atmung ad Kreislauf beteiligten Gebietes an der ventralen Oberflache der Medulla oblongata durch Kalteblockade. Pflügers Arch. Eur. J. Physiol. **297:** 201–220, 1967.
304. SCHLAFKE, M. E., SEE, W. R., AND LOESCHCKE, H. H.: Ventilatory response to alterations of H^+ ion concentration in small areas of the ventral medullary surface. Respir. Physiol. **10:** 198–212, 1970.
305. SCHMIDT, D. E.: Effects of thyrotropin-releasing hormone (TRH) on pentobarbital induced decrease in cholinergic neuronal activity. Commun. Psychopharmacol. **1:** 469–473, 1977.
306. SCHMITT, H., SCHMITT, H., AND FENARD, S.: Action of α-adrenergic blocking drugs on the sympathetic centres and their interactions with central sympathoinhibitory effects of clonidine. Arzneim.-Forsch. **23:** 40–45, 1973.
307. SCHOENE, R. B., HALTER, J. B., AND PIERSON, D. J.: Correlation of catecholamine release and ventilatory responses to hypoxia and hypercapnia. Fed. Proc. **41:** 1102, 1982.
308. SGARAGLI, G., AND PAVAN, F.: Effects of amino acid compounds injected into cerebrospinal fluid spaces on colonic temperature, arterial blood pressure and behaviour of the rat. Neuropharmacology **11:** 45–56, 1972.
309. SIMANTOV, R., KUHAR, M. J., UHL, G. R., AND SNYDER, S. H.: Opioid peptide enkephalin immunohistochemical mapping in rat central nervous system. Proc. Natl. Acad. Sci. U.S.A. **74:** 2167–2171, 1977.
310. SNEAD, O. C.: Minireview. Gamma hydroxybutyrate. Life Sci. **20:** 1935–1944, 1977.
311. SNEAD, O. C., AND BEARDEN, L. J.: Naloxone overcomes the dopaminergic, EEG, and behavioral effects of γ-hydroxybutyrate. Neurology **30:** 832–838, 1980.
312. SNYDER, S. H.: Brain peptides as neurotransmitters. Science **209:** 976–983, 1980.

313. Snyder, S. H., Young, A. B., Oster-Granite, M. L., and Herndon, R. M.: Glutamic acid, a putative neurotransmitter of cerebellar granule cells: Evidence from the virally induced granuloprival cerebellum. *In* Metabolic Compartmentation and Neurotransmission, ed. by S. Berl, D. D. Clarke, and D. Schneider, pp. 1–10, Plenum Press, New York, 1975.
314. Sokoll, M. D., Hoyt, J. L., and Gergis, S. D.: Studies in muscle rigidity, nitrous oxide, and narcotic analgesic agents. Anesth. Analg. **51:** 16–20, 1972.
315. Sokoloff, P., Martres, M. P., and Schwartz, J. C.: Three classes of dopamine receptor (D-2, D-3, D-4) identified by binding studies with ^{3}H-apomorphine and ^{3}H-domperidone. Naunyn-Schmiedebergs Arch. Pharmakol. **315:** 89–102, 1980.
316. Sole, M. J., Vanloon, G. R., Shum, A., Lixfield, W., and McGregor, D. C.: Left ventricular receptors inhibit brain serotonin neurons during coronary artery occlusion. Science **201:** 620–622, 1978.
317. Snider, R. S., and Niemer, W. T.: A Sterotoxic Atlas of the Cat Brain, Univ. Chicago Press, Chicago, 1961.
318. Speck, D. F., and Feldman, J. L.: The effects of microstimulation and microlesions in the ventral and dorsal respiratory groups in medulla of cat. J. Neurosci. **2:** 744–757, 1982.
319. St. John, W. M.: Characterization of tidal volume regulation function of the pneumotaxic center. Respir. Physiol. **18:** 64–79, 1973.
320. Steel, G. C.: Clinical application of gamma hydroxybutyric acid as a sleep cover in lumbar epidural block. Proc. Roy. Soc. Med. **61:** 825–826, 1968.
321. Strombom, U.: Catecholamine receptor agonists. Effects on motor activity and rate of tyrosine hydroxylation in mouse brain. Naunyn-Schmiedebergs Arch. Pharmakol. **292:** 167–176, 1976.
322. Suzman, M. M.: The use of beta-adrenergic blockade with propranolol in anxiety syndromes. Postgrad. Med. J. suppl. 47, 104–108, 1971.
323. Svensson, T. H., and Thoren, P.: Brain noradrenergic neurons in the locus coeruleus: Inhibition by blood volume load through vagal afferents. Brain Res. **172:** 174–178, 1979.
324. Swanson, L. W., and Hartman, B. K.: The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. J. Comp. Neurol. **163:** 467–505, 1975.
325. Takabashi, H., Tiba, M., Ino, M., and Takayasu, T.: The effects of γ-aminobutyric acid on blood pressure. Jpn. J. Physiol. **5:** 334–339, 1955.
326. Takigawa, M., and Mogenson, G. J.: A study of inputs to antidromically identified neurons of the locus coeruleus. Brain Res. **135:** 217–230, 1977.
327. Talman, W. T., Perrone, M. H., and Reis, D. J.: Evidence for L-glutamate as the neurotransmitter of baroreceptor afferent nerve fibers. Science **209:** 813–814, 1980.
328. Talman, W. T., Perrone, M. H., and Reis, D. J.: Acute hypertension after the local injection of kainic acid into the nucleus tractus solitarii of rats. Circ. Res. **48:** 292–298, 1981.
329. Talman, W. T., and Reis, D. J.: Baroreflex actions of substance P microinjected into nucleus tractus solitarii in rat: A consequence of local distortion. Brain Res. **220:** 402–407. 1981.
330. Toleikis, J. R., Wang, L., and Boyarsky, L. L.: Effects of excitatory and inhibitory amino acids on phasic respiratory neurons. J. Neurosci. Res. **4:** 225–235, 1979.
331. Uhl, G. R., Goodman, R. R., Kuhar, M. J., Childers, S. R., and Snyder, S. H.: Imunohistochemical mapping of enkephalin containing cell bodies, fibers and nerve terminals in the brain stem of the rat. Brain. Res. **166:** 75–94, 1979.
332. Valtin, H., and Tenney, S. M.: Respiratory adaptation to hyperthyroidism. J. Appl. Physiol. **15:** 1107–1112, 1960.
333. van der Heyden, J. A. M., Dekloet, E. R., Korf, J., and Versteeg, D. H. G.: GABA content of discrete brain nuclei and spinal cord of the rat. J. Neurochem. **33:** 857–861, 1979.
334. Vandermaelen, C. P., and Aghajanian, G. K.: Intracellular studies showing modulation of facial motorneurone excitability by serotonin. Nature (Lond.) **287:** 346–347, 1980.
335. Versteeg, D. H., van der Gutgen, J., de Jong, W., and Palkovits, M.: Regional concentrations of noradrenaline and dopamine in rat brain. Brain Res. **113:** 563–574, 1976.
336. Vibert, J. F., Caille, D., Bertrand, F., Gromysz, H., and Hugelin, A.: Ascending projection from the respiratory centre to mesencephalon and diencephalon. Neurosci. Lett. **11:** 29–33, 1979.
337. Virus, R. M., Knuepfer, M. M., McManus, D. Q., Brody, M. J., and Gebhart, G. F.: Capsaicin treatment in adult male Wistar-Kyoto and spontaneously hypertensive rats: Effects on nociceptive behaviour and cardiovascular regulation. Eur. J. Pharmacol. **72:** 209–217, 1981.
338. Vogel, R. A., Frye, G. D., Wilson, J. H., Kuhn, C. M., Mailman, R. B., Mueller, R. A., and Breese, G. R.: Attenuation of the effect of punishment by thyrotropin releasing hormone: Comparisons with chlordiazepoxide. J. Pharmacol. Exp. Ther. **212:** 153–161, 1980.
339. von Euler, C., Hayward, J. N., Marttila, I., and Wyman, R. J.: Respiratory neurones of the ventrolateral nucleus of the solitary tract of cat: Vagal input, spinal connections and morphological identification. Brain Res. **61:** 1–22, 1973.
340. von Euler, C., Marttila, I., Remmers, J. E., and Trippenbach, T.: Effect of lesions on the parabrachial nucleus on the mechanisms for central and relex termination of inspiration in the cat. Acta Physiol. Scand. **96:** 324–337, 1976.
341. von Euler, C., and Trippenbach, T.: Excitability changes of the inspiratory "off switch" mechanism tested by electrical stimulation of nucleus parabrachialis in the cat. Acta Physiol. Scand. **97:** 175–188, 1976.
342. von Euler, U. S. and Gaddum, J. H.: An unidentified depressor substance in certain tissue extracts. J. Physiol. (Lond.) **72:** 74–87, 1931.
343. von Euler, U. S., and Pernow, B.: Neurotropic effects of substance P. Acta Physiol. Scand. **36:** 265–275, 1956.
344. Waldrop, T. G., Millhorn, D. E., and Eldridge, F. L.: Long-lasting central inhibition of respiration: Mediation by GABA and endogenous opiates. Physiologist **24:** 102, 1981.
345. Wang, S. C., and Ngai, S. H.: General organization of central respiratory mechanisms. *In* Handbook of Physiology, Section 3: Respiration, vol. 1, ed. by W. O. Fenn and H. Rahn, pp. 482–505, American Physiological Society, Washington, DC, 1964.
346. Wang, S. C., and Ward, J. W.: "Analeptics." Pharmacol. Ther. B **3:** 123–165, 1977.
347. Wardlaw, S. L., Stark, R. I., Baxi, L., and Frantz, A. G.: Plasma β-endorphin and β-lipotropin in the human fetus at delivery: Correlation with arterial pH and pO_2. J. Clin. Endocrinol. Metab. **49:** 888–891, 1979.
348. Wasserman, K.: Breathing during exercise. N. Engl. J. Med. **298:** 780–781, 1978.
349. Wasserman, K., Mitchell, R. A., Berger, A. J., and Casaburi, R.: Mechanism for the isoproterenol hyperpnea in the anesthetized cat. Fed. Proc. **39:** 904, 1978.
350. Weil, J. V., Byrne-Quinn, E., Sodal, E. I., Kline, J. E., McCollough, R. E., and Filley, G. F.: Augmentation of chemosensitivity during mild exercise in normal man. J. Appl. Physiol. **33:** 813–819, 1972.
351. Weil, J. V., McCullough, R. E., Kline, J. S., and Sodal, I. E.: Diminished ventilatory response to hypoxia and hypercapnia after morphine in man. N. Engl. J. of Med. **292:** 1103–1106, 1975.
352. Weinberger, S., Gabel, R., Steinbrook, R., Leith, D., and V. Fencl.: Ventilatory response to CO_2 breathing after adrenergic blockade in goats. Fed. Proc. **41:** 1506, 1982.
353. Weinstock, M., Roll, D., Erez, E., and Baher, M.: Physostigmine antagonizes morphine-induced respiratory depression but not analgesia in dogs and rabbits. Br. J. Anaesth. **52:** 1171–1176, 1980.
354. Welsh, M. J., Heistad, D. D., and Abboud, F. M.: Depression of ventilation by dopamine in man. J. Clin. Invest. **61:** 708–713, 1978.
355. Werman, R., Davidoff, R. A., and Aprison, M. H.: Inhibition of motoneurones by iontophoresis of glycine. Nature (Lond.) **214:** 681–683, 1967.
356. Westlund, K. N., and Coulter, J. D.: Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: Axonal transport studies and dopamine-β-hydroxylase immunocytochemistry. Brain Res. Rev. **2:** 235–264, 1980.
357. Whelan, R. F. and Young, I. M.: The effect of adrenaline and noradrenaline infusions on respiration in man. Br. J. Pharmacol. **8:** 98–102, 1953.
358. Widdicombe, J. G. (ed.): Respiratory Pharmacology. Pergamon Press, Elmsford, NY, 1980.
359. Wiener, W. J., Goetz, C. G., Nausieda, P. A., and Klawans, H. L.: Respiratory dyskinesias: Extrapyramidal dysfunction and dyspnea. Ann. Intern. Med. **88:** 327–331, 1978.
360. Winokur, A., and Utiger, R. D.: Thyrotropin-releasing hormone: Regional distribution in rat brain. Science **185:** 265–267, 1974.
361. Wyman, R. J.: Neural generation of the breathing rhythm. Annu. Rev. Physiol. **39:** 417–448, 1977.
362. Yaksh, T. L., Jessel, T. M., Gamse, R., Mudge, A. W., and Leeman, S. E.: Intrathecal morphine inhibits substance P release from mammalian spinal cord *in vivo*. Nature (Lond.) **286:** 155–157, 1980.
363. Yaksh, T. L., and Rudy, T. A.: Analgesia mediated by a direct spinal action of narcotics. Science **192:** 1357–1358, 1976.
364. Yamada, K. A., Hamosh, P., and Gillis, R. A.: Respiratory depression produced by activation of GABA receptors in hindbrain of cat. J. Appl. Physiol. **51:** 1278–1286, 1981.
365. Yammamoto, Y., Lagercrantz, H., and von Euler, C.: Effects of substance P and TRH on ventilation and pattern of breathing in newborn rabbits. Acta Physiol. Scand. **113:** 541–543, 1981.
366. Yarbrough, G. G., and Singh, D. K.: Intravenous thyrotropin releasing hormone (TRH) enhances the excitatory actions of acetylcholine (ACh) on rat cortical neurons. Experientia (Basel) **34:** 390, 1978.
367. Younes, M., and Polacheck, J.: Temporal changes in effectiveness of a constant inspiratory-terminating vagal stimulus. J. Appl. Physiol. **50:** 1183–1192, 1981.
368. Young, A. B., and Snyder, S. H.: Strychnine binding in rat spinal cord membranes associated with the synaptic glycine receptor: Cooperativity of glycine interactions. Mol. Pharmacol. **10:** 790–809, 1974.
369. Youngblood, W. W., Lipton, M. A., and Kizer, J. S.: TRH-like immunoreactivity in urine, serum, and extrahypothalamic brain: Non-identity with synthetic pyroglu-hist-pro-NH_2 (TRH). Brain Res. **151:** 99–116, 1978.
370. Zaleska, M.: Effect of pentobarbital anesthesia on serotonin metabolism in hypoxic rat brain. Pol. J. Pharmacol. Pharm. **31:** 179–186, 1979.
371. Zobrist, R. H., Allerton, H. W., and Isom, G. E.: Characterization of the respiratory activity of (D-Ala^2) methionine-enkephalinamide. Eur. J. Pharmacol. **70:** 121–128, 1981.