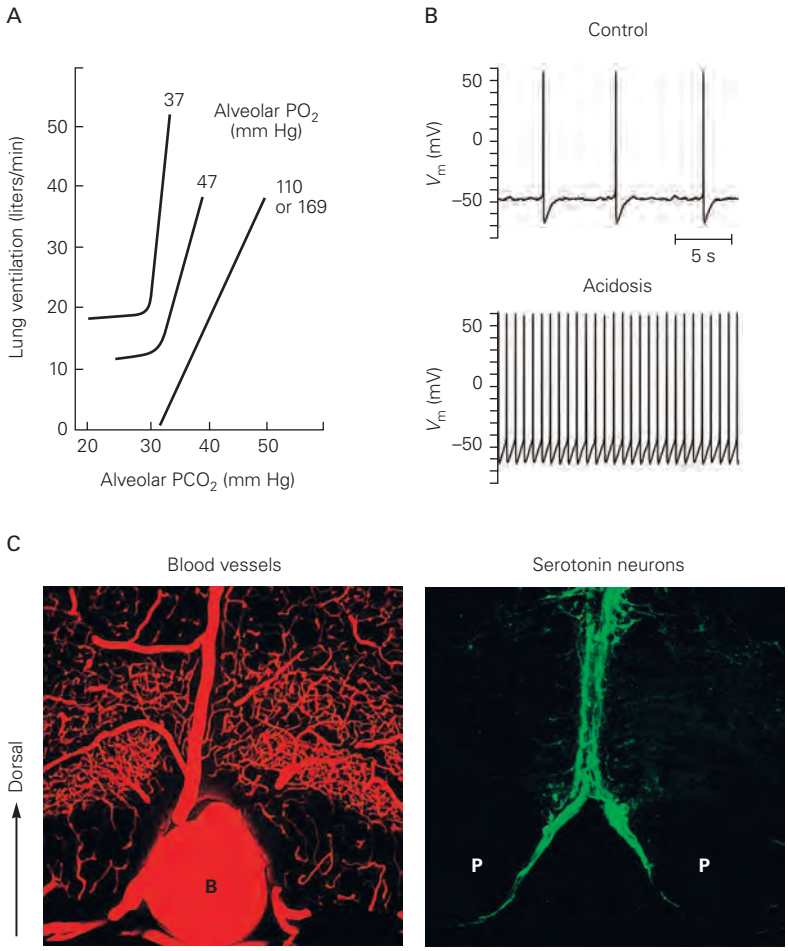


Figure 40–9 Respiratory motor output is regulated by carbon dioxide in the blood.

A. Lung ventilation (determined by the rate and depth of breathing) in humans is steeply dependent on the partial pressure of carbon dioxide (PCO_2) at normal levels of the partial pressure of oxygen (PO_2) (>100 mm Hg). When PO_2 drops to very low values (<50 mm Hg), breathing is stimulated directly and also becomes more sensitive to an increase in PCO_2 (seen here as an increase in the slope of the curves for alveolar PO_2 of 37 and 47 mm Hg). (Reproduced, with permission, from Nielsen and Smith 1952.)

B. Central chemoreceptors in the medulla control ventilatory motor output to maintain normal blood CO_2. The firing rate of serotonergic neurons within the raphe nuclei of the medulla increases when elevated PCO_2 causes a pH decrease. The records shown here are from in vitro recordings of a neuron in the raphe nuclei of a rat at two different levels of pH (7.4, control, and 7.2, acidosis). (Reproduced, with permission, from Wang et al. 2002.)

C. Serotonergic neurons are closely associated with large arteries in the ventral medulla where they can monitor local changes in PCO_2. Two images of the same transverse section of the rat medulla show blood vessels after injection of a red fluorescent dye into the arterial system (*left*) and green antibody staining for tryptophan hydroxylase, the enzyme that synthesizes serotonin (*right*). The basilar artery (**B**) is on the ventral surface of the medulla between the pyramidal tracts (**P**). (Reproduced, with permission, from Bradley et al. 2002. Copyright © 2002 Springer Nature.)

accompanying decrease in pH. The most sensitive area for this is along the ventral surface of the medulla lateral to the pyramidal tract. This region contains at least two sets of neurons that respond to elevated CO_2. Glutamatergic neurons in the retrotrapezoid nucleus in the rostral ventrolateral medulla, near the facial motor nucleus, are highly sensitive to CO_2 levels. Absence of these neurons, due to a mutation in the phox2b transcription factor required for their development, causes congenital central hypoventilation syndrome, in which there is failure to breathe adequately, particularly during sleep. In addition, serotonergic neurons in the rostral ventrolateral medulla, like retrotrapezoid neurons, lie along penetrating arteries and are sensitive to acidosis (Figure 40–9B,C). Genetic deletion of these neurons reduces the ventilatory response to hypercapnia, especially during sleep. Recent studies demonstrate that a serotonin 5-HT_{2A} agonist can restore arousal responses to CO_2, suggesting that the serotonergic neurons play a modulatory role, increasing the sensitivity of the CO_2 reflexes during hypercapnia, and that this may be especially important during sleep.

The motor pattern generated by the respiratory system is remarkably stable in healthy people, but a variety of diseases can alter these patterns. One of the most common and easily recognized patterns is Cheyne-Stokes respiration, which is characterized by repeated cycles of gradually increasing then decreasing ventilation, alternating with cessation of breathing (apnea). This periodic breathing is seen, for example, in congenital central hypoventilation syndrome, where the central neurons are not sufficiently sensitive to rising CO_2, particularly during sleep. By the time they begin to respond, CO_2 levels may already be quite high. This causes hyperventilation, which reduces CO_2 levels below the threshold where breathing is required. The result is a period of apnea, until the CO_2 levels again become quite high (Figure 40–10).

A similar pattern is seen in people who have cardiac or pulmonary disease that increases the time it takes for the change in alveolar CO_2 to register with the medulla. Cheyne-Stokes respiration often occurs in hospitalized patients with marginal cardiac or respiratory reserve when they fall asleep, thus reducing

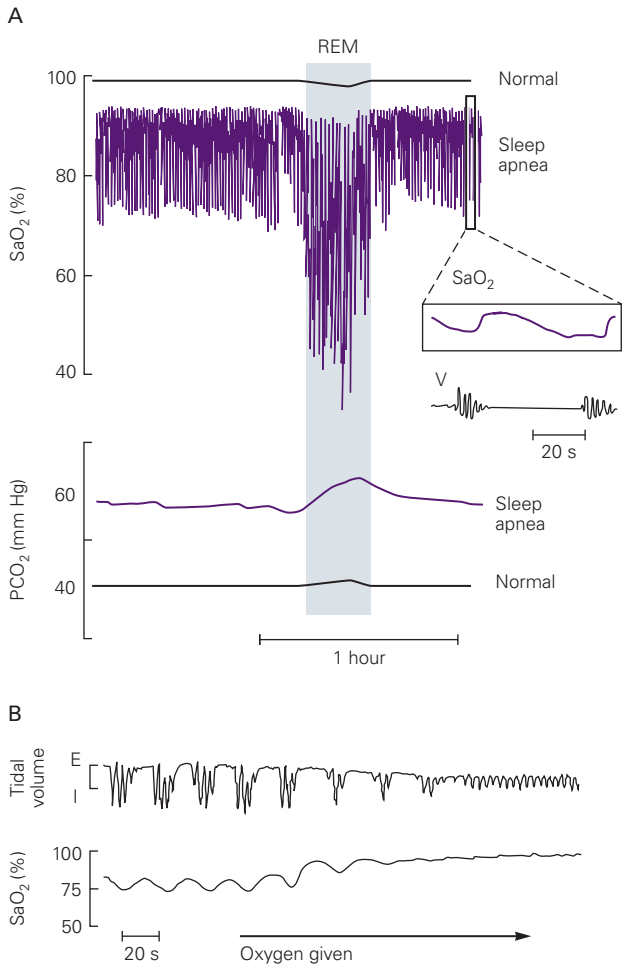


Figure 40–10 Respiratory motor patterns can become unstable during sleep.

A. Sleep apnea (cessation of breathing) is a common problem that often goes undetected. The records here show blood oxygen saturation (SaO_2) and CO_2 partial pressure (PCO_2) during sleep in a healthy person and a patient with obstructive sleep apnea. In the healthy person, SaO_2 remains near 100%, and PCO_2 remains near 40 mm Hg during both rapid eye movement (REM) and non-REM sleep. In the patient with sleep apnea, reduced muscle tone (hypotonia) during sleep leads to collapse of the upper airway, resulting in obstruction and apnea. Repetitive apnea at the rate of approximately once per minute causes the patient's SaO_2 to fall repetitively and dramatically. (The inset shows a period of approximately 80 seconds on an expanded scale. Ventilation [V] begins at the nadir of the SaO_2 and again ceases when the blood oxygen increases.) During non-REM sleep, the patient's PCO_2 increases to near 60 mm Hg. During REM sleep, the SaO_2 and PCO_2 become even more abnormal, as worsening airway hypotonia causes greater obstruction. Many people with sleep apnea wake up repeatedly during the night because of the apnea, but the arousals are too brief for them to be aware that their sleep is interrupted. (Adapted, with permission, from Grunstein and Sullivan 1990.)

B. Breathing in most normal individuals becomes unstable during sleep at high altitudes. The upper trace shows an example of a Cheyne-Stokes breathing pattern in a healthy person, during the first night after arriving at an altitude of 17,700 feet, where the low partial pressure of oxygen in the air reduces the blood SaO_2 to approximately 75% to 80%. Repeated cycles of waxing and waning ventilation are separated by periods of apnea. Administration of supplemental oxygen results in a rapid return to a normal respiratory pattern. This abnormal pattern disappears in most people after they have acclimated to the altitude. (Reproduced, with permission, from Lahiri et al. 1984.)

other behavioral drives for respiration. Although not dangerous in itself, it can indicate that there is a serious underlying cardiorespiratory problem that needs to be corrected.

Other inputs to the respiratory pattern generator come from the circuitry mediating particular behaviors, as breathing must be coordinated with many motor actions that share the same muscles. To accomplish this coordination, respiratory neurons in the medulla receive input from neuronal networks concerned with vocalization, swallowing, sniffing, vomiting, and pain. For example, the ventral respiratory group is connected with a part of the parabrachial complex in the pons termed the *pontine respiratory group* or *pneumotaxic center*. These pontine neurons coordinate breathing with behaviors such as chewing and swallowing. They can cause holding of the breath at full inspiration (called *apneusis*), which is required during eating and drinking. The reserve of air in the lungs permits a cough, if necessary, to expel any food or drink that may enter the airway. Other neurons in the intertrigeminal zone, between the motor and principal sensory trigeminal nuclei, receive facial and upper airway sensory inputs and project to the ventrolateral medulla to temporarily stop breathing to protect against accidental inspiration of dust or water.

Voluntary motor pathways can take over the control of breathing during talking, eating, singing, swimming, or playing a wind instrument. Descending inputs cause hyperventilation at the onset of exercise, in anticipation of an increase in oxygen demand. In fact, this leads to a sustained drop in blood CO_2 during exercise—the opposite of what would be expected for a negative feedback control system. Other descending inputs from the limbic system produce hyperventilation in connection with pain or anxiety and, in some people, may be responsible for causing spontaneous panic attacks, characterized by hyperventilation and a feeling of suffocation. These various descending inputs allow efficient integration of breathing with

other behaviors, but they ultimately must yield to the need to maintain blood gas homeostasis, as even a small increase in CO_2 produces severe air hunger or *dyspnea*. Thus, the respiratory control system is a fascinating example of a brain stem pattern generator that must be sufficiently stable to ensure survival yet flexible enough to accommodate a wide variety of behaviors.

Monoaminergic Neurons in the Brain Stem Modulate Sensory, Motor, Autonomic, and Behavioral Functions

In addition to containing the primary sensory and motor nuclei of the cranial nerves and the reflex and pattern generator mechanisms that control basic behaviors, the brain stem also contains a set of modulatory cell groups. In a groundbreaking series of experiments in the 1970s, Hans Kuypers used the newly discovered method of retrograde transport of axonal tracers to identify the cell groups in the brain stem and diencephalon that contribute to modulation of spinal cord sensory and motor systems and those that send inputs directly to the cerebral cortex. To a surprising extent, these two sets of experiments, starting at opposite ends of the neuraxis, identified a common substrate whose role it is to modulate circuitry at other levels of the nervous system, almost as if it were an "autonomic system" for the brain.

These cell groups have direct connections to the forebrain, brain stem, and spinal cord that regulate the overall level of function of their targets. Like the way serotonergic neurons set the overall sensitivity of CO_2 reflexes, brain stem monoaminergic modulatory systems adjust the overall responsiveness of a wide variety of sensory systems by means of projections to sensory neurons in the spinal cord and brain stem, including nociceptive systems. Descending projections from these modulatory systems also control motor tone, which is critical for adjusting posture and gait as well as initiating finer movements. Ascending inputs to the forebrain control overall arousal as well as responses to rewarding situations. While these modulatory systems are not sufficient to accomplish motor, sensory, or cognitive tasks on their own, their ability to adjust the responsiveness of these systems plays an enormously influential role in overall behavior.

Many Modulatory Systems Use Monoamines as Neurotransmitters

The monoaminergic systems use decarboxylated derivatives of the cyclic amino acids tyrosine, tryptophan, and histidine as neurotransmitters. They were among the first in the brain to be identified and mapped due to the property that some of them possess to fluoresce when exposed to formaldehyde. In the 1960s, Dahlstrom and Fuxe used this property to identify serotonergic, noradrenergic, and dopaminergic cell groups in the brain stem. In the 1970s, with the development of immunohistochemical methods able to map the enzymes that synthesize monoamines, other investigators mapped neurons containing epinephrine and histamine.

The cell groups of these modulatory systems in general were unlike earlier identified nuclei in the brain. Rather than forming compact clusters of cell bodies, the monoaminergic cell groups tended to form columns that extended longitudinally through the brain stem and hypothalamus (see Figure 40–6). The monoamine systems were therefore designated with letters and numbers, to avoid confusion with other systems of nomenclature for the brain (Figure 40–11).

The first cell groups identified by Dahlstrom and Fuxe were simply identified alphabetically as the "A" cell groups, and then numbered sequentially from caudal to rostral. It was later determined that the A1–A7 cell groups produce norepinephrine and the A8–A14 groups produce dopamine. The A1, A3, and A5 designations were applied to neurons located in the ventrolateral corner of the medullary and pontine tegmentum (the A3 group was quite small and the term is no longer used), while the A2, A4, A6, and A7 names were applied to cell groups located more dorsally, similar to the columns of motor neurons in the brain stem (Figure 40–11A). The A1 and A2 groups, located among the neurons of the nucleus ambiguus and the nucleus of the solitary tract (respectively), are mainly concerned with autonomic functions. Together, they modulate hypothalamic and brain stem systems that regulate the autonomic nervous system. The noradrenergic A4–A7 cell groups have widespread influence over sensory and motor systems, ranging from the cerebral cortex to the spinal cord, and provide important modulation of arousal and wakefulness.

The dopaminergic systems (Figure 40–11E) include the A8–A10 cell groups, located in the midbrain in and near the substantia nigra, that modulate motor systems as well as forebrain mechanisms of reward and motivation. The A11 and A13 dopaminergic neurons, in the dorsal hypothalamus, provide input to sensory, motor, and autonomic systems in the brain stem and spinal cord. The A12, A14, and A15 neurons have a neuroendocrine role, including release of dopamine as a pituitary release-inhibiting hormone for prolactin secretion. The A16 cell group modulates olfactory inputs, and the A17 neurons in the retina modulate vision.

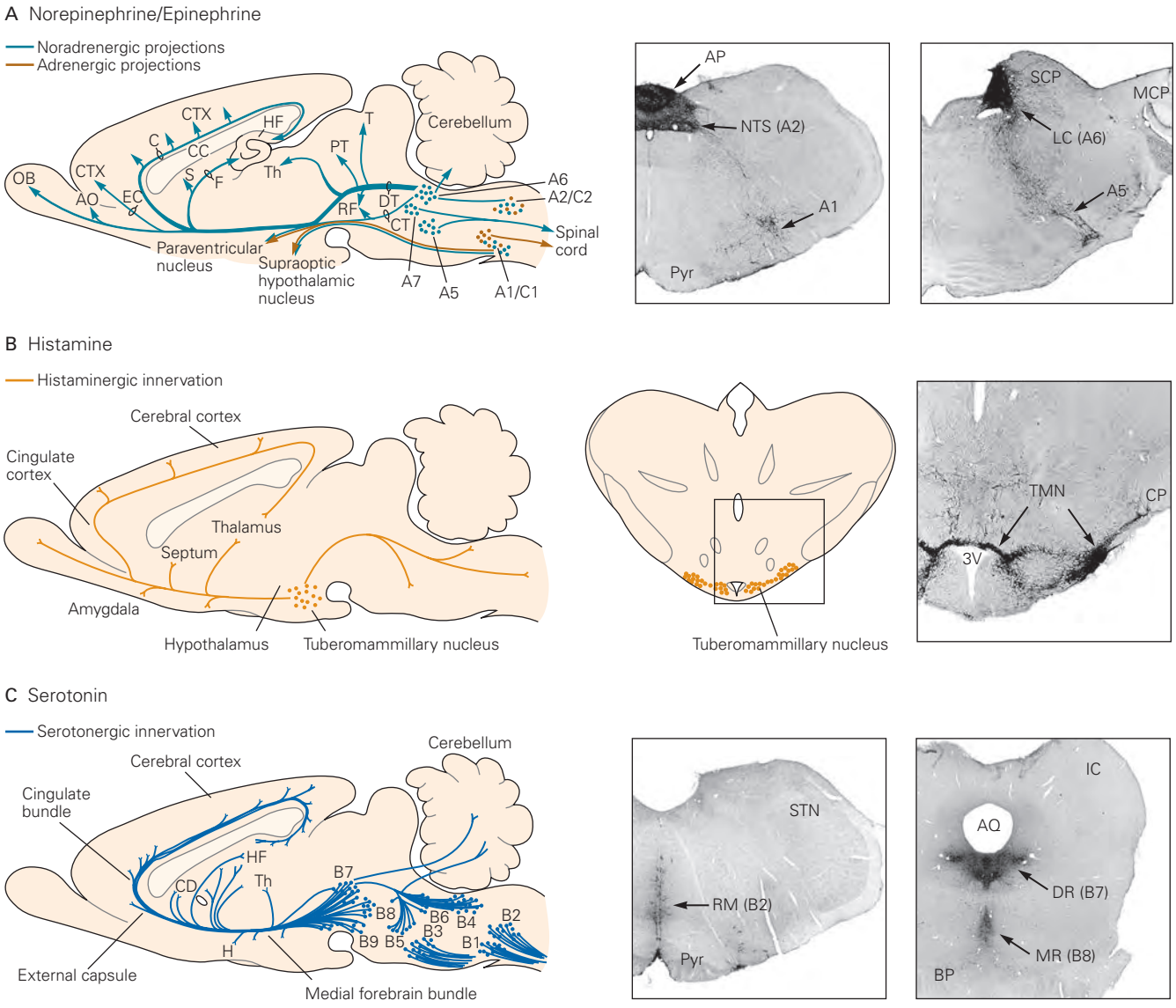


Figure 40–11 Locations and projections of monoaminergic and cholinergic neurons in the rat brain. (Abbreviations: **3V**, third ventricle; **AC**, anterior commissure; **AP**, area postrema; **AQ**, Sylvian aqueduct; **ARC**, arcuate nucleus; **BM**, nucleus basalis of Meynert; **BP**, brachium pontis; **CD**, caudate; **CP**, cerebral peduncle; **DBh**, horizontal limb of the diagonal band; **DR**, dorsal raphe; **FX**, fornix; **IC,** inferior colliculus; **LC**, locus ceruleus; **LDT**, laterodorsal tegmental nucleus; **MCP**, middle cerebellar peduncle; **MGN**, medial geniculate nucleus; **MR**, median raphe; **MS**, medial septum; **MTT**, mammillothalamic tract; **NTS**, nucleus tractus solitarius; **OC**, optic chiasm; **PPT**, pedunculopontine tegmental nucleus; **PUT**, putamen; **Pyr**, pyramidal tract; **RM**, raphe magnus; **SC**, superior colliculus; **SCP**, superior cerebellar peduncle; **SN**, substantia nigra; **STN**, spinal trigeminal nucleus; **TMN**, tuberomammillary nucleus; **VTA**, ventral tegmental area.)

A. Noradrenergic neurons (A groups) and adrenergic neurons (C groups) are located in the medulla and pons. The A2 and C2 groups in the dorsal medulla are part of the nucleus of the solitary tract. The A1 and C1 groups in the ventral medulla are located near the nucleus ambiguus. Both groups project to the hypothalamus; some C1 neurons project to sympathetic preganglionic neurons in the spinal cord and control cardiovascular and endocrine functions. The A5, A6 (locus ceruleus), and A7 cell groups in the pons project to the spinal cord and modulate autonomic reflexes and pain sensation. The locus ceruleus also projects rostrally to the forebrain and plays an important role in arousal and attention.

B. All histaminergic neurons are located in the posterior lateral hypothalamus, mostly within the tuberomammillary nucleus. These neurons project to virtually every part of the neuraxis and play a major role in arousal.

C. Serotonergic neurons (B groups) are found within the medulla, pons, and midbrain, mostly near the midline in the raphe nuclei. Those within the medulla (the B1–B4 groups corresponding to the raphe magnus, raphe obscurus, and raphe pallidus) project throughout the medulla and spinal cord and modulate afferent pain signals, thermoregulation, cardiovascular control, and breathing. Those within the pons and midbrain (the B5–B9 groups in the raphe pontis, median raphe, and dorsal raphe) project throughout the forebrain and contribute to arousal, mood, and cognition.

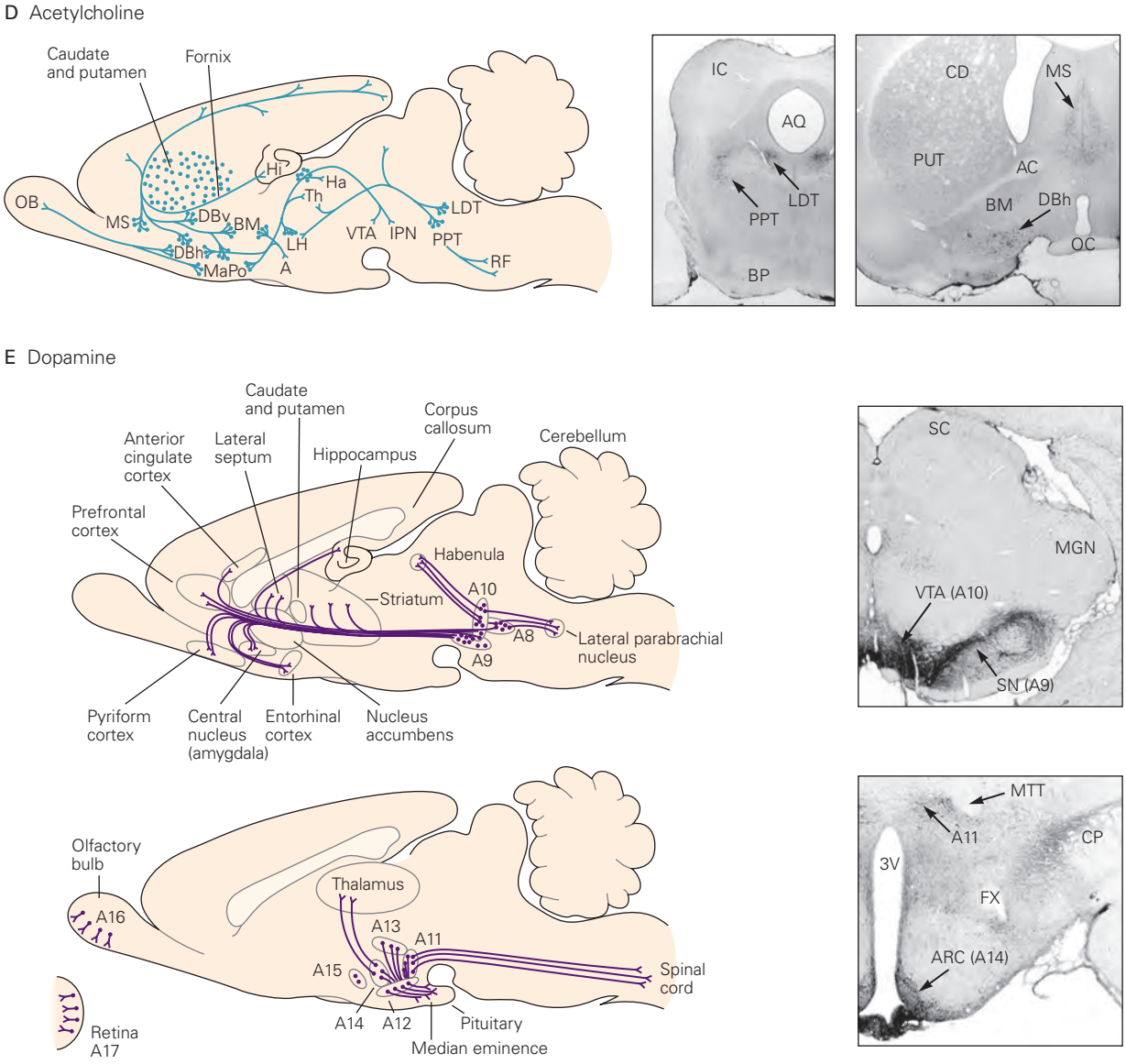


Figure 40–11 (*Continued*) **D.** Cholinergic neurons (sometimes called Ch groups) are located in the pons, midbrain, and basal forebrain. Those in the pons and midbrain (mesopontine groups) are divided into a ventrolateral cluster (pedunculopontine nucleus) and the dorsomedial cluster (laterodorsal tegmental nucleus). The mesopontine cholinergic neurons project to the brain stem reticular formation and the thalamus. Those in the basal forebrain are divided into the medial septum, the nuclei of the vertical and horizontal limbs of the diagonal band, and the nucleus basalis of Meynert. These neurons project throughout the cerebral cortex, hippocampus, and amygdala. Both groups play an important role in arousal, and the basal forebrain groups are also involved in more selective attention.

E. Dopaminergic neurons are located in the midbrain and hypothalamus. The dopaminergic cell groups were originally included with the noradrenergic cell groups and are still labeled as A groups (A8–A17). The A8 group is in the midbrain dorsally adjacent to the substantia nigra. The A9 cell group constitutes the substantia nigra pars compacta. These two groups of neurons project to the striatum and play an important role in initiation of movement. The A10 group is located in the ventral tegmental area just medial to the substantia nigra. These cells project to the frontal and temporal cortex and limbic structures of the basal forebrain and play a role in emotion and memory. The A11 and A13 cell groups in the zona incerta of the hypothalamus project to the lower brain stem and spinal cord and regulate sympathetic preganglionic neurons. The A12, A14, and A15 cell groups are components of the neuroendocrine system. Some of them inhibit release of prolactin into the hypophysial portal circulation, and others control gonadotrophin secretion. Dopaminergic neurons are also found in the olfactory bulb (A16) and the retina (A17).

The B cell groups, which had a slightly different color of fluorescence, were found to produce serotonin. They are associated with the midline raphe cell groups in the pons and medulla (Figure 40–11C). The B1–B4 cell groups in the medulla mainly provide descending modulation of sensory, motor, and autonomic neurons in the brain stem and spinal cord. The B5–B7 neurons in the pons mainly provide serotonergic innervation of the thalamus, hypothalamus, and cerebral cortex. The functions of serotonin in modulating these targets can be quite complex to decipher, mainly because there are at least 14 different serotonin receptors, and different ones can be expressed by different cell types in a target area.

A few years after the A and B cell groups were named, immunohistochemical studies demonstrated that some medullary neurons have the enzymes to make dopamine and norepinephrine but do not fluoresce. These neurons, named cell groups C1–C3, were found to process these other catecholamines to adrenalin, or epinephrine. They are closely related to the A1–A3 cell groups in the medulla (Figure 40–11A).

Histaminergic cell groups are mainly found in the tuberomammillary nucleus and adjacent areas of the posterior hypothalamus (near the mammillary body) and are named E1–E5 (Figure 40–11B). They are the sole source of histaminergic actions in the entire brain, from the cerebral cortex to the spinal cord, and are involved in a variety of arousal responses.

Although cholinergic neurons are not, strictly speaking, monoaminergic, some of them also participate in modulatory systems, and these have been numbered Ch1–Ch6 (Figure 40–11D). This classification system did not include the many other cholinergic neurons in the nervous system, such as motor neurons or striatal interneurons, and is not used much anymore. Rather, scientists refer to the cholinergic neurons by their location, eg, the pedunculopontine (Ch6) and laterodorsal tegmental (Ch5) neurons in the pons, which project widely from the cerebral cortex to the medulla, and the basal forebrain (Ch1–Ch4) groups, which project to the cerebral cortex, hippocampus, and amygdala.

Monoaminergic Neurons Share Many Cellular Properties

Neurons that use monoamines as neurotransmitters have many similar electrophysiological properties. For example, most continue to fire spontaneous action potentials in a highly regular pattern when isolated from their synaptic inputs in brain slice preparations. Their action potentials typically are followed by a slow membrane depolarization that leads to the next spike (Figure 40–12). The spontaneous regular firing pattern of monoaminergic neurons is regulated by intrinsic pacemaker currents (Chapter 10). Tonic firing in vivo may be important for ensuring continuous delivery of monoamines to targets. For example, the basal ganglia depend on continuous exposure to dopamine from the neurons of the substantia nigra to facilitate motor responses.

The properties of monoaminergic neurons are suited to their unique and widespread modulatory roles in brain function. Indeed, some axon terminals of monoaminergic cells do not even form conventional synaptic connections, instead releasing neurotransmitter diffusely to many targets at once. Most

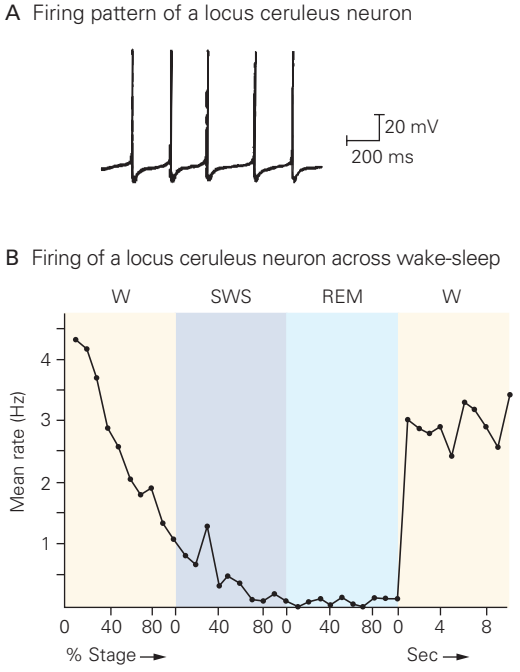


Figure 40–12 Monoaminergic neurons have similar firing patterns across the wake–sleep cycle.

A. When monoaminergic neurons are isolated from synaptic input, they fire spontaneously at a regular rate. This recording is from a noradrenergic neuron in the locus ceruleus. Action potentials are followed by a characteristic afterhyperpolarization followed by a slow depolarization to the next spike, producing a pacemaker-like activity (Chapter 10). Serotonergic and histaminergic neurons exhibit similar spontaneous activity.

B. All three monoaminergic cell types show similar patterns of firing across the wake–sleep cycle. The plot shows that a locus ceruleus neuron in a rat fires fastest when the animal is awake (**W**), slows down as wakefulness wanes and during slow-wave sleep (**SWS**), and almost completely ceases to fire during rapid eye movement (**REM**) sleep. (Adapted, with permission from Aston-Jones and Bloom 1981. © Society for Neuroscience.)

monoaminergic neurotransmission occurs by means of metabotropic synaptic actions through G protein–coupled receptors. Many monoaminergic neurons co-release neuropeptides, which have slow effects through other G protein–coupled receptors. Thus, although some monoaminergic synaptic actions involve fast synaptic mechanisms (Chapter 13), many involve slower metabotropic and neuromodulatory pathways as well (Chapter 14).

Autonomic Regulation and Breathing Are Modulated by Monoaminergic Pathways

Neurons in the adrenergic C1 group in the rostral ventrolateral medulla play a key role in maintaining resting vascular tone as well as adjusting vasomotor tone necessitated by various behaviors. For example, an upright posture disinhibits neurons in the rostral ventrolateral medulla that directly innervate the sympathetic preganglionic vasomotor neurons, thus increasing vasomotor tone to prevent a drop in blood pressure (the baroreceptor reflex). Neurons in the noradrenergic A5 group in the pons inhibit the sympathetic preganglionic neurons and play a role in depressor reflexes (eg, the fall in blood pressure in response to deep pain).

Serotonin regulates many different autonomic functions including gastrointestinal peristalsis, thermoregulation, cardiovascular control, and breathing. Electrical stimulation of serotonergic neurons within the medullary raphe nuclei increases heart rate and blood pressure. Serotonergic neurons in the medulla also project to neurons in the medulla and spinal cord that regulate breathing, as described earlier.

The role of serotonergic neurons as CO_2 receptors may explain why defects in the serotonergic system have been linked to sudden infant death syndrome (SIDS) (Figure 40–13A). SIDS is the leading cause of postneonatal mortality in the Western world, responsible for six infant deaths every day in the United States. A widely held theory holds that some SIDS cases are due to defective CO_2 chemoreception, breathing, and arousal. A relatively high number of serotonergic neurons are found in the raphe nuclei of infants who die of SIDS, but these have an immature morphology, and they are associated with relatively low serotonin levels and low serotonergic receptor densities.

A plausible neurobiological mechanism for SIDS is that a defect in development of serotonergic neurons leads to reduced ability to detect a rise in partial pressure of CO_2 when airflow is obstructed during sleep, thus blunting the normal protective response, which includes arousal and increased ventilation (Figure 40–13C). Infants sleeping face down would be unable to arouse sufficiently to change position when bedding blocks the airway. The Back to Sleep campaign, which encourages parents to place infants on their backs when put down to sleep, has reduced the incidence of SIDS by 50%.

Pain Perception Is Modulated by Monoamine Antinociceptive Pathways

Although pain is necessary for an animal to minimize injury, continued pain following an injury may be maladaptive (eg, if the pain prevents vigorous escape from

Figure 40–13 (Opposite) Serotonergic neurons have a role in the response to a rise in CO_2 levels as well as sudden infant death syndrome.

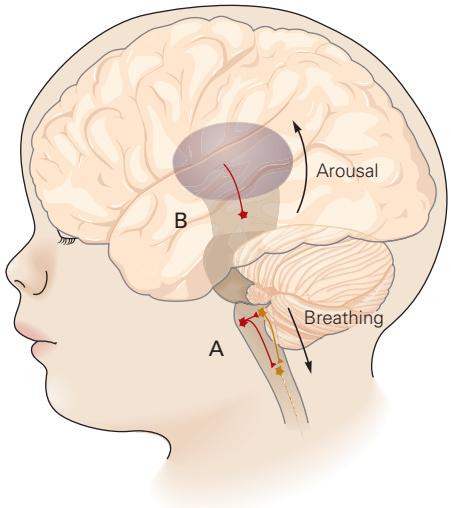
A. Serotonergic neurons in the medulla are central respiratory chemoreceptors that are thought to stimulate breathing in response to an increase in arterial blood PCO_2 (partial pressure of CO_2). The dendrites of these neurons wrap around large arteries and are stimulated by an increase in PCO_2 (see Figure 40–9C). They project to and excite motor neurons in the medulla and spinal cord that control breathing.

B. Serotonergic neurons in the midbrain are also PCO_2 sensors. Shown here is the increase in firing rate of a serotonergic neuron from the dorsal raphe nucleus in response to an increase in PCO_2 (monitored by the resultant decrease in external pH). This increase in firing rate may sensitize ascending arousal pathways from the parabrachial nucleus, which also receives input from other CO_2 sensory pathways. This important response prevents suffocation during sleep when the airway is obstructed. (Reproduced, with permission, from Richerson 2004. Copyright © 2004 Springer Nature.)

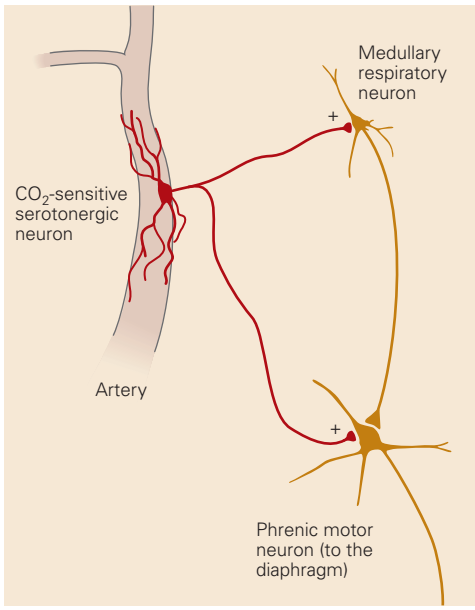
C. Sudden infant death syndrome (SIDS).

1. *Triple risk hypothesis of SIDS*. Infants are at risk to die from SIDS when three conditions coincide. First, the infant must be vulnerable because of an underlying abnormality of the brain stem, such as a genetic predisposition or an environmental insult (eg, exposure to cigarette smoke). Second, the baby must be in the stage of development (usually 2–6 months of age) when it may be difficult to change position to escape suffocation. Third, there also must be an exogenous stressor (eg, lying face down in a pillow). (Reproduced, with permission from, Filiano and Kinney 1994. © 1994 S. Karger AG.)

2. *Proposed mechanism of SIDS*. The combination of abnormal serotonergic neurons (eg, from exposure to cigarette smoke) and postnatal immaturity of neurons involved in respiratory control leads to the inability to respond effectively to airway obstruction (eg, from lying face down in a crib). The infant then does not wake up and turn its head or breathe faster, either of which would correct the problem. As a result, blood oxygenation decreases severely (hypoxia) while blood CO_2 rises (hypercapnia).



A Serotonergic neurons



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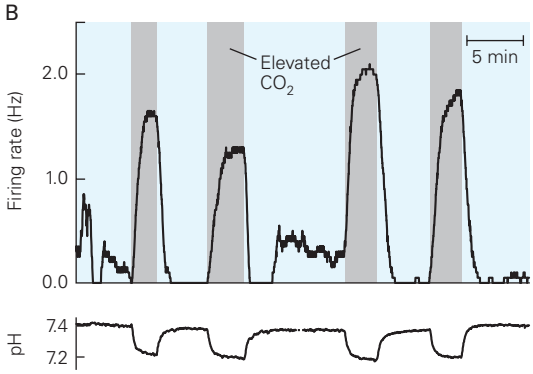
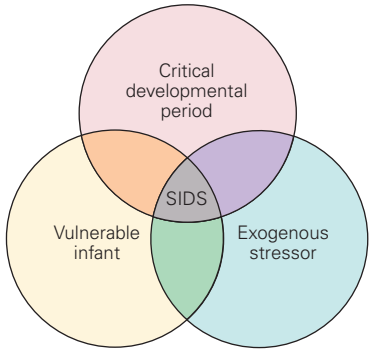
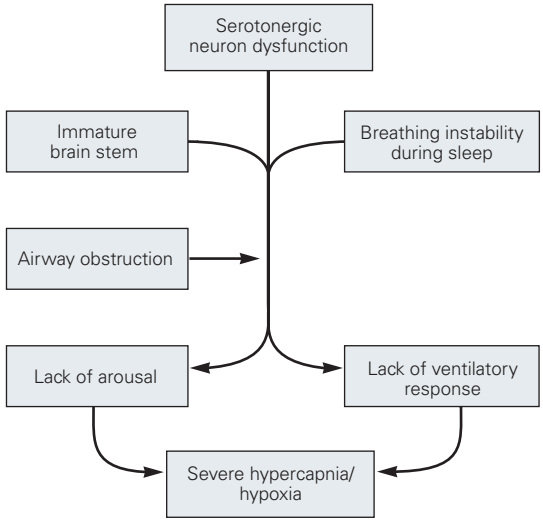


C Sudden Infant Death Syndrome

1 Triple risk hypothesis



2 Proposed mechanism



a predator). The monoaminergic systems include important descending projections to the dorsal horn of the spinal cord that modulate pain perception (Chapter 20).

The noradrenergic inputs to the spinal cord originate from the pontine cell groups A5–A7, with the locus ceruleus (A6) providing most of the input to the dorsal horn. Similarly, the serotonergic raphe nuclei in the medulla, particularly the nucleus raphe magnus, project to the dorsal horn where they modulate the processing of information about noxious stimuli. Direct application of serotonin to dorsal horn neurons inhibits their response to noxious stimuli, and intrathecal administration of serotonin attenuates the defensive withdrawal of the paw evoked by noxious stimuli. In addition, intrathecal administration of antagonists of serotonin receptors blocks the pain inhibition evoked by stimulation of the raphe nuclei.

Insight into the role of serotonin in pain processing has been used in treating migraine headaches. In particular, the triptan agonists of 5-HT_{1D} receptors have been found to be therapeutically effective. One of the possible mechanisms of action of this family of tryptamine-based drugs includes presynaptic inhibition of pain afferents from the meninges, preventing sensitization of central neurons. Drugs that block monoamine reuptake, including both traditional antidepressants and selective serotonin reuptake inhibitors, are effective in limiting pain in patients with chronic pain and migraine headaches.

Motor Activity Is Facilitated by Monoaminergic Pathways

The dopaminergic system is critical for normal motor performance. A massive projection ascends from the substantia nigra pars compacta to the striatum, where dopaminergic fibers act on striatal neuron receptors to release inhibition of motor responses (Chapter 38).

Patients with Parkinson disease in whom midbrain dopaminergic neurons have degenerated have trouble initiating movement and difficulty sustaining movements. Such patients speak softly, write with small letters, and take small steps. Conversely, drugs that facilitate dopaminergic transmission in the striatum can result in unintended behaviors, ranging from motor tics (small muscle twitches), to chorea (large-scale, jerky limb movements), to complex cognitive behaviors (such as compulsive gambling or sexual activity).

As first shown by Sten Grillner, serotonergic neurons play an important role in modulating motor programs. Drugs that activate serotonin receptors can induce hyperactivity, myoclonus, tremor, and rigidity, all of which are part of the "serotonin syndrome." Increases in the firing of raphe neurons have been observed in animals during repetitive motor activities such as feeding, grooming, locomotion, and deep breathing. Conversely, the firing of both serotonergic raphe and noradrenergic locus ceruleus neurons practically ceases during the atonia and lack of movement that occur during rapid eye movement (REM) sleep.

Noradrenergic cell groups in the pons also send extensive projections to motor cell groups. This modulatory input acts on presynaptic β- and α_1-adrenergic receptors to facilitate excitatory inputs to motor neurons (Chapter 31). The sum of these effects is to facilitate motor neuron responses in stereotypic and repetitive behaviors such as rhythmic chewing, swimming, or locomotion. Conversely, increased β-adrenergic activation during stress can exaggerate motor responses and produce tremor. Drugs that block β-adrenergic receptors are used clinically to reduce certain types of tremor and are often taken by musicians prior to performances to minimize tremulousness.

Ascending Monoaminergic Projections Modulate Forebrain Systems for Motivation and Reward

The forebrain is continuously bombarded with sensory information and must determine which stimuli deserve attention. It must also decide which of many available behaviors should receive priority, based in part on experience—which behaviors have achieved rewarding outcomes in the past. The ascending monoaminergic systems play key roles in modulating all of these choices.

As noted earlier, dopaminergic inputs to the striatum adjust the likelihood that a specific motor pattern or even a cognitive pattern will be expressed. Low dopamine levels reduce output from the direct pathway striatal neurons (which release behaviors) and increase activity of indirect pathway striatal neurons (which inhibit behavior). Dopamine also has been linked to reward-based learning. Rewards are objects or events for which an animal will work (Chapter 42) and are useful in positively reinforcing behavior. Activity of dopaminergic neurons increases when a reward (such as food or juice) is unexpectedly given. But after animals are trained to expect a reward following a conditioned stimulus, the activity of the neurons increases immediately after the conditioned stimulus rather than after the reward. This pattern of activity indicates that dopaminergic neurons provide a reward-prediction error signal, an important element in reinforcement learning. The importance of dopamine in learning is also supported by observations that lesions of dopaminergic systems prevent reward-based learning.