Hormones and Breathing*

Tarja Saaresranta, MD, PhD, and Olli Polo, MD, PhD

A number of hormones, including hypothalamic neuropeptides acting as neurotransmitters and neuromodulators in the CNS, are involved in the physiologic regulation of breathing and participate in adjustment of breathing in disease. In addition to central effects, some hormones also control breathing at peripheral chemoreceptors or have local effects on the lungs and airways. Estrogen and progesterone seem to protect from sleep-disordered breathing, whereas testosterone may predispose to it. Progesterone and thyroxine have long been known to stimulate respiration. More recently, several hormones such as corticotropin-releasing hormone and leptin have been suggested to act as respiratory stimulants. Somatostatin, dopamine, and neuropeptide Y have a depressing effect on breathing. Animal models and experimental human studies suggest that also many other hormones may be involved in respiratory control.

(CHEST 2002; 122:2165–2182)

Key words: control of breathing; dopamine; estrogen; hormones; insulin-like growth factor-1; leptin; progesterone; respiration; somatostatin; thyroxine

Abbreviations: AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; CRH = corticotropin-releasing hormone; EMG = electromyogram; FSH = follicle-stimulating hormone; GABA = γ-aminobutyric acid; GH = growth hormone; GHRH = growth hormone-releasing hormone; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; IGF = insulin-like growth factor; LH = luteinizing hormone; MPA = medroxyprogesterone acetate; OSAS = obstructive sleep apnea syndrome; REM = rapid eye movement; SaO2 = arterial oxygen saturation; SWS = slow-wave sleep; THR = thyrotropin-releasing hormone; VIP = vasoactive intestinal peptide

A textbook of endocrinology from 1985 stated that "respiration does not have a significant element of endocrine control."1 With growing body of evidence on the interaction of respiration and hormones during the past 15 years, this statement has subsequently been omitted.2 Today, the control of respiration encompasses both voluntary (cortex) and involuntary (emotional, metabolic, neural, and endocrine components) control mechanisms.

The endocrine and nervous systems have complex interactions. The nervous system produces and liberates biochemical agents, which may act as locally or systemically via circulation. Several hormones serve as neurogenic mediators within the CNS. Circulating hormones can have local or autocrine effects in the cells in which they are produced. Locally synthesized hormones can diffuse into adjacent or nearby cells to exert paracrine effects. The effect of a single hormone can differ in various tissues or in the same tissue at different eras of life span. The presence of other hormonal or nonhormonal regulators may reinforce or hinder the action of a hormone. Most complex processes under endocrine control, such as respiration, are influenced by several hormones.

Respiration as a vital function is not regulated by specific hormones but is influenced by a wide array of hormones. The current bulk of evidence suggests that hormones have an important role in the regulation of breathing via several mechanisms. They may stimulate breathing (Table 1) at the level of the CNS or at peripheral chemoreceptors (eg, progesterone; Fig 1) or by altering the basic metabolic rate, affecting indirectly also breathing (eg, thyroid hormones). The long-term indirect effects of hormones on breathing include adjustment for the acid-base balance, body temperature, and mass of muscle and fat. Endocrine agents may also have an effect on the upper or lower airway patency. They may reduce upper airway collapsibility during sleep (eg, progesterone) or may have bronchodilatory (eg, epinephrine) or bronchoconstrictive (eg, histamine) effects
Obstructive sleep apnea syndrome (OSAS) affects serum hormone levels, which may be recuperated with nasal continuous positive airway pressure (CPAP) treatment (Table 3). The prevalence of sleep-disordered breathing is increased in several endocrine disorders and after menopause (Tables 4, 5). However, these prevalence estimates should be interpreted cautiously because well-done epidemiologic studies are lacking in most endocrine disorders, and definition of sleep apnea varies between studies, resulting in wide variations in prevalence rates.

Some respiratory effects of hormones have been known for decades. Hyperventilation and decreased PaCO₂ was first described during pregnancy; later on, the same phenomenon was confirmed during the luteal phase of the menstrual cycle. The effect of progesterone on breathing was confirmed 5 decades ago. Ventilatory responses differ between genders and vary according to the menstrual cycle phase. Women tend to have lower ventilatory responses than men. The hypercapnic ventilatory response (HCVR) is higher during the luteal phase than the follicular phase of the menstrual cycle. Except for the effects of progesterone on breathing, the effect of the deficiency of the thyroid hormones on breathing has also been known for decades.

A number of other hormones, including hypothalamic neuropeptides acting as neuromodulators and neurotransmitters in the CNS, have an impact on the control of breathing. Some hormones regulate breathing also at peripheral chemoreceptors or have local effects on the lungs and airways. Recent observations suggest that leptin may have a role in obesity-related hypoventilation and in OSAS.

### Somatotropic Axis

#### Growth Hormone

Growth hormone-releasing hormone (GHRH) increases and somatostatin decreases the secretion of growth hormone (GH). GHRH appears to be the common physiologic factor stimulating slow-wave

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21985/ on 06/26/2017)
Table 3—Various Hormones in OSAS, and the Effect of Nasal CPAP Therapy on Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>OSAS Effects</th>
<th>Effect of Nasal CPAP</th>
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<tbody>
<tr>
<td>GH</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>LH</td>
<td>Decreased or no change</td>
<td>Unknown</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Decreased or no change</td>
<td>Increased or no change</td>
</tr>
<tr>
<td>Prolactin</td>
<td>No change</td>
<td>Decreased or no change</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Increased or no change</td>
<td>Decreased or no change</td>
</tr>
<tr>
<td>Leptin</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Substance P</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

sleep (SWS) and GH release.36 GH secretion depends on age, gender, phase of the menstrual cycle, pubertal status, nutritional state, quality of sleep, physical exercise, and body composition.35 Visceral fat has a powerful negative feedback on GH secretion.37 For each 1.5 kg/m² increase in body mass index, there is a 50% decrease in the 24-h secretion of GH.37 The 24-h plasma GH profile consists of low stable GH levels superimposed by secretory bursts, the most reproducible one in adults occurring in deep sleep shortly after sleep onset.38,39

Nocturnal secretory pulse amplitude and the total 24-h secretion of GH decrease with increasing age.40,41 Basal and stimulated GH secretions are greater in women than in men throughout adulthood until women achieve menopause. In elderly women and men, the effects of both gender and age on GH secretion markedly diminish.42 Across of span of adulthood, levels of serum testosterone and estradiol positively determine both mean GH levels and GH-secretory burst mass.37 The data on the interactions of GH and breathing are essentially limited to observations in patients with sleep-disordered breathing or COPD. In patients with OSAS, GH secretion is decreased.43–45 Improving nasal breathing in snorers increases nocturnal GH release.46 The decreased GH appears not to be associated primarily with obesity-related low GH release because CPAP treatment increases the amount of secreted GH within a few hours.44,45 The increase in GH secretion during CPAP therapy is attributed to a CPAP-induced increase in SWS.47 Altered pattern of breathing per se may also enhance GH secretion, since hyperventilation or breath-holding increase GH secretion in healthy young male patients.48

There are some reports on using GH therapy to improve pulmonary function. A case report of a man with end-stage COPD and prolonged weaning suggested that a high-dose (27 IU/d, 0.3 IU/kg body weight daily) therapy with human recombinant GH may increase serum insulin-like growth factor (IGF)-1 and peak expiratory flow rate within a few days, and respiratory muscle strength within 10 days.49 Further, in seven patients with COPD, maximal inspiratory pressure improved after a 3-week GH treatment, but FEV₁, FVC, PaO₂, PaCO₂, and arterial pH remained unchanged.50 In contrast, in a randomized controlled study in patients with adult-onset GH deficiency, low doses (0.5 to 1 IU/d) of human recombinant GH did not improve pulmonary function or respiratory muscle strength despite a significant increase in IGF-1 concentrations.51 There are at least two possible factors explaining the discrepancy. First, the different response may be due to various doses of administered human recombinant GH. Second, the patients with COPD had severely impaired pulmonary function and respiratory muscle strength, whereas the patients with GH deficiency had almost normal pulmonary function and inspiratory muscle strength, and therefore no further improvement could be expected.

Table 4—Prevalence of Sleep Apnea in Some Endocrine Disorders and States

<table>
<thead>
<tr>
<th>Endocrine Disorders</th>
<th>Prevalence of Sleep Apnea</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes, type 1</td>
<td>19 to 42%</td>
<td>Rees et al.,1981</td>
</tr>
<tr>
<td>Diabetes, type 2</td>
<td>1.9% (vs 0.3% in nondiabetics)</td>
<td>Katsunata et al.,1991</td>
</tr>
<tr>
<td>Diabetes with autonomic neuropathy</td>
<td>0 to 38%</td>
<td>Rees et al.,1981</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>25 to 100%</td>
<td>Bajaj et al.,1984</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>9 to 93%</td>
<td>Hart et al.,1985</td>
</tr>
<tr>
<td>Cushing disease/ syndrome</td>
<td>45%</td>
<td>Sholery et al.,1992</td>
</tr>
<tr>
<td>Poly cystic ovary syndrome</td>
<td>17 to 44%</td>
<td>Sholery et al.,1992</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>2.7%* (vs 0.6% in premenopausal women)</td>
<td>Bixler et al.,2001</td>
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</table>

*Prevalence in women is without hormone-replacement therapy.
Prader-Willi syndrome is a disorder with various manifestations of hypothalamic insufficiency. Major findings include infantile hypotonia, mental retardation, behavior disorder, facial abnormalities, obesity, hypogonadism, short stature, abnormal respiratory responses, and OSAS. In children with Prader-Willi syndrome, GH treatment increases ventilation, central inspiratory drive, airway occlusion pressure, and HCVR. Since the improvement of ventilation does not correlate with the decrease in body mass index, improved inspiratory muscle strength has been suggested as the mechanism of action.

**IGF-1**

IGF-1 (somatomedin-C) has a long half-life of 21 to 40 h. It is produced mainly in the liver, but also in a wide array of extrahepatic tissues. Cultured fibroblasts derived from human lung are able to produce IGF-1. IGF-1 is tightly bound to its binding proteins in plasma. GH stimulates IGF-1 secretion but also the production of IGF-1 binding proteins. IGF-1 mediates the anabolic growth-promoting effects of GH in the muscle. Starvation decreases whereas a good nutritional state increases IGF-1 concentrations. IGF-1 has several endocrine interactions. Endogenous estradiol and GH are potent stimulators of IGF-1 expression in specific target tissues. IGF-1 also enhances the stimulatory effects of estradiol. Exogenous estrogens appear to have a biphasic effect on IGF-1. Low doses of estrogen increase IGF-1, whereas high doses decrease IGF-1.

IGF-1 levels decrease with age. In healthy men, every 7 additional years after the age of 18 to 21 years equals an approximately 50% decrease in IGF-1. In women, IGF-1 decrease is less rapid before menopause but accelerates during postmenopause. Healthy women after natural menopause have lower IGF-1 levels than age-matched premenopausal women. Modified from Biber and coworkers.

Oxygen content of breathing air appears to contribute to the secretion of IGF-1. In rats, hyperoxia increases the expression of IGF-1 and its type I receptor. Chronic hypoxemia in newborn lambs is associated with decrease in IGF-1 without change in GH.

The literature provides evidence that IGF-1 and respiratory drive are linked, either through a common controller or through interactive mechanisms (Table 6). IGF-1 receptors are located around the central chemoreceptors in the brainstem, and also in the cerebellum where the inputs from chemoreceptors are integrated. Simultaneous increases of progesterone, IGF-1, and ventilation observed in pregnancy in the luteal phase of the menstrual cycle, or during progesterin therapy in postmenopausal women suggest that IGF-1 could be involved in progesterone-induced ventilatory stimulation. The increased levels of IGF-1 in acromegalic individuals seem to determine the increased drive for breath-
ing, which manifests as increased HCVR measured during wakefulness \(^7\) or increased frequency of central sleep apnea \(^7\) or periodic breathing with symmetric waxing and waning respiratory efforts. \(^6\)

Analogous to GH, serum IGF-1 levels respond with increase to treatment of sleep-disordered breathing. Serum IGF-1 concentrations and the amount of SWS increase after adenotonsillectomy in children with OSAS. \(^7\) In adult snorers, improved nasal breathing increases IGF-1 levels. \(^4\) The more severe OSAS is, the more IGF-1 is depressed, until relieved with nasal CPAP therapy. \(^5\)

Somatostatin

Somatostatin is the inhibitory counterpart of GHRH in GH release. IGF-1 stimulates somatostatin while somatostatin reduces GH-dependent IGF-1 production. Somatostatin suppresses central respiratory drive in animals. \(^5\) Presuming a similar action in humans, somatostatin may be involved in the pathophysiology of sudden infant death syndrome. The increased release of somatostatin in the elderly \(^5\) might also explain some of the increase in sleep-disordered breathing with age. These hypotheses are supported by recent observations in humans. The number of somatostatin binding sites was increased in respiratory nuclei of the brainstem in victims of sudden infant death syndrome, suggesting a deficit of the hypoxic ventilatory response (HVR). \(^5\)

In adult humans, somatostatin infusion decreases HVR and peripheral (fast) HCVR. \(^7\)

**REPRODUCTIVE HORMONES**

Progesterone is a potent respiratory stimulant, whereas the role of the other reproductive hormones in the control of breathing is not established. The multiple location of progesterone, estrogen, androgen, prolactin, and human chorionic gonadotropin/luteinizing hormone receptors suggests that these hormones might act locally in various tissues, including trachea, lungs, brain, and brainstem, \(^5\) and thereby possibly be involved also in breathing.

Ventilatory responses differ between genders. In premenopausal women, ventilatory responses are increased during the luteal vs the follicular phase of the menstrual cycle. However, they are lower than in men irrespective of menstrual cycle phase. \(^5\) In men, the HVR is positively correlated with resting oxygen consumption. In women, no such correlation has been observed. During sleep, the hypoxic response decreases less in women than in men, resulting in disappearance of the gender-related differences in ventilatory control. \(^5\)

After menopause, women seem no longer to be protected from sleep-disordered breathing (Table 5). \(^5\) although some studies have found no impact of menopause per se. \(^5\) In their pioneering study, Block and coworkers \(^5\) observed markedly more apneic events and oxygen desaturation in postmenopausal women. In men, the prevalence of sleep-disordered breathing increases throughout adult life, \(^5\) whereas in women it becomes apparent only after 50 years of age. \(^5\) Apneic events were most prevalent among women > 55 years of age and among those who already had reached menopause. \(^5\) Although menopause seems to affect breathing, the length of time since menopause seems to have no impact. \(^5\)

Harman and coworkers \(^5\) found that none of the obese premenopausal women desaturated during sleep, whereas all men except one with hypogonadism desaturated. During wakefulness, premenopausal women have higher genioglossal muscle activity compared with age-matched men, \(^5\) possibly due to progesterone. \(^5\) Postmenopausal sleep-disordered breathing may be related to decreased ventilatory drive due to decreased production of female hormones, whereas in premenopausal women structural abnormalities may predominate as etiologic factors. However, endocrine abnormalities behind menstrual irregularities in premenopausal women with sleep-disordered breathing may also have an impact on breathing \(^5\) and on possibly decreased ventilatory drive.

**Follicle-Stimulating Hormone and Luteinizing Hormone**

The cessation of ovarian function abolishes the negative feedback of estradiol and progesterone to follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, resulting in an increase of

![Table 6—Interactions of Serum IGF-1 Levels and Various Factors or States Directly or Indirectly Related to Breathing](http://www.chestjournal.org/)
these gonadotropins. In patients with OSAS, serum LH levels may be decreased or normal. Men with COPD have higher LH concentrations than control subjects, and some of them also have increased FSH levels. In postmenopausal women with respiratory impairment, decrease in FSH and LH concentrations occurs simultaneously with the ventilatory improvement, suggesting that these hormones might directly or indirectly be involved in control of ventilation.

**Progesterone**

The stimulatory effect on breathing of endogenous progesterone and the synthetic medroxyprogesterone acetate (MPA) are established by several studies. Other endogenous progestins such as pregnanolone have not been studied. Increased secretion of progesterone explains hyperventilation and low CO2 during pregnancy, and also during the luteal phase of the menstrual cycle. The cyclic respiratory changes cease after menopause. Block and coworkers found that 60% of postmenopausal women had nocturnal desaturation, hypopneas, or apneas, whereas only 11% of premenopausal women had such events. It has been suggested that in regularly menstruating women, hypopneas are rarest during the mid-luteal phase when progesterone and estrogen are highest, although these findings have not been confirmed by others. During pregnancy, oxygenation is well maintained, and sleep-disordered breathing may even decrease.

Perhaps by increasing the respiratory drive in general, progesterone also improves the upper airway function. Peak phasic and tonic genioglossus activities are higher in premenopausal than in postmenopausal women and higher during the luteal phase than the follicular phase of the menstrual cycle, whereas upper airway resistance does not differ. Progesterone concentrations correlate positively with both tonic and phasic genioglossal electromyogram (EMG) activity. Combined estrogen and progesterone therapy increases genioglossal EMG activity in postmenopausal women. Premenopausal women are resistant to induction of sleep-disordered breathing by ethanol ingestion, possibly due to the protective effect of progesterone on the upper airway patency. Further, ethanol decreases peak integrated genioglossal EMG activity during the follicular phase but not during the luteal phase of the menstrual cycle, also suggesting the protective effect of progesterone. The beneficial effects of progesterone on the upper airway function and breathing are supported by animal studies. In decerebrate cats, pretreatment with progestin decreases the alcohol-induced mismatching of hypoglossal and phrenic activities. Progesterone receptor messenger RNA content in the rabbit lung is

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21985/)

**Figure 2.** Effect of progestin (MPA) administration on HVR. During normocapnia, MPA increased chemosensitivity (left). During MPA-induced hypocapnia (right), HVR did not differ from that with placebo. VE = minute ventilation; STPD = standard temperature and pressure, dry; l/min = liters per minute; NS = not significant. Used with permission from Zwillich et al.103

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regulated by sex steroids and changes according to the physiologic concentrations of estradiol and progesterone.\textsuperscript{111}

Synthetic progestins (MPA and chlormadinone acetate) have been used for respiratory stimulation with variable success. A few studies have reported some improvement in sleepiness, blood gas levels, and in number or duration of apneic and hypopneic events.\textsuperscript{112,113} All but one of the study subjects were males. In postmenopausal women, MPA monotherapy improved the maximum duration of apneic events.\textsuperscript{104} However, these women did not have OSAS. Treatment with MPA, 60 mg/d, for 2 weeks improved ventilation in postmenopausal women with partial upper airway obstruction during sleep, but tended to be less effective in reducing apnea-hypopnea index (AHI) than nasal CPAP.\textsuperscript{114} There are no studies evaluating the efficacy of progestin monotherapy on female patients with OSAS. Chlormadinone acetate, 25 mg bid, for 7 days decreases AHI and increases arterial oxyhemoglobin saturation ($S_aO_2$) and HCVR. The degree of improvement in awake load response and HCVR correlates positively with improvement in sleep-disordered breathing.\textsuperscript{115,116}

Estrogens

In fertile women, estrogens are mainly in a form of estradiol derived from the ovaries. After menopause, the major estrogen is estrone, produced by the adrenals\textsuperscript{132} and by the peripheral adipose tissues through aromatization of androgens, mainly androstenedione.\textsuperscript{133} Estradiol, like testosterone, is mainly bound to sex hormone-binding globulin.

Regularly menstruating women have the lowest frequency of episodes of hypopnea during the midluteal phase when progesterone and estrogen are highest.\textsuperscript{104} Estradiol is needed for up-regulation of progesterone receptors,\textsuperscript{117} which are likely to mediate the respiratory effects of progesterone. Oral estrogen therapy at doses used to control postmenopausal vasomotor symptoms may decrease AHI and increase lowest oxygen desaturation related to apneic events.\textsuperscript{121} The prevalence of sleep apnea is lower in postmenopausal estrogen users than in those without any hormone replacement therapy (1.5% vs 5.5%; Table 6). Postmenopausal women using hormone replacement therapy (estrogen monotherapy or estrogen combined with progestins) had less bronchial obstruction, which was not explained by smoking or other factors.\textsuperscript{134} However, estrogens may deteriorate breathing in patients with asthma. Estrogen replacement therapy worsened asthma symptoms in postmenopausal women with mild-to-moderate asthma and increased consumption of bronchodilators.\textsuperscript{135} Another recent study reported a weak but consistent positive association between hormone replacement therapy and self-reported asthma and asthma-like symptoms.\textsuperscript{136} In the same study, no association was found between the use of oral contraceptive pills and asthma. Estrogen-induced bronchospasm in a postmenopausal woman with severe obstructive airways disease has also been reported.\textsuperscript{137}

Testosterone

Testosterone is a male sex hormone, but small concentrations are also found in female subjects. Testosterone is the only androgen that has been
attributed to control of breathing, although its role is unclear. With age, free testosterone decreases and LH increases, but the total testosterone levels remain essentially unchanged.138

The role of testosterone is controversial in sleep-disorder breathing. The male preponderance of OSAS94 suggests that testosterone could be involved. In a study of seven obese men, all but the hypogonadal man had nocturnal hypoxemia or sleep-disorder breathing.36 Exogenous testosterone may suppress139 or increase140,141 HVR resulting in sleep apnea both in male139–142 and in female subjects143 without change in weight, sleep stage distribution, or sleep duration.141 In contrast to men with no change in upper airway dimensions during testosterone administration,141 an increase in supraglottic resistance in women receiving androgen therapy may reflect anatomic changes.143 In a nonobese 70-year-old woman, a testosterone-producing ovarian tumor caused sleep apnea that was resolved after removal of the tumor.144 Androgens down-regulate estrogen and progesterone receptors,131 and also increase estrone levels but not estradiol or progesterone levels.145 Down-regulation of progesterone receptors may therefore weaken the respiratory stimulant effect of progesterone in men.

However, the degree of respiratory disturbance appears to be associated with decreased overnight plasma free testosterone, but this relationship is lost after age adjustment.138 Testosterone increases HVR and metabolic rate.146 In male patients with chronic respiratory failure, serum testosterone concentrations correlate positively with PaO2.147 Glucocorticoid treatment decreases serum free testosterone in men with COPD.148 Among male patients with OSAS, those with severe desaturation exhibited delayed peak testosterone concentrations.149 In OSAS, free and total testosterone as well as sex hormone-binding globulin are decreased, while LH remains within normal limits.75,150 The endocrine abnormality is reversed after a 3-month CPAP therapy.75 However, normal levels of testosterone have also been observed in patients with OSAS without any effect from CPAP treatment.100

Some studies have found no effect of testosterone on nocturnal breathing. In men with OSAS, androgen blockade with flutamide did not have any effect on sleep-disordered breathing or chemosensitivity.151 In patients receiving hemodialysis, there was no change in AHI on testosterone therapy after a 2-month washout period.152 However, 75% of the patients with a clinical history of OSAS were receiving testosterone therapy, compared to only 35% of those without such a history.152 It is not known whether this mirrors the effect of testosterone per se, or perhaps the severity of underlying renal failure and its effects on the acid-base balance and respiratory compensation.

**Prolactin**

Prolactin secretion is regulated by several factors. Thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), oxytocin, and angiotensin II increase prolactin release, whereas dopamine and γ-aminobutyric acid (GABA) inhibit its secretion.153 In premenopausal women, serum prolactin levels are higher than in postmenopausal women or men.154 Actually, pulsatile prolactin secretion is similar in postmenopausal women and in men. Estrogens stimulate prolactin gene transcription155 and increase prolactin concentrations by increasing the pulsatile secretion of prolactin.156 The higher levels of prolactin in premenopausal women have been linked with the higher estrogen levels.156

Prolactin is assumed to stimulate surfactant production in the lung.86,87,157 Some evidence suggests that prolactin may be involved in breathing in adults, either directly or indirectly. In healthy premenopausal women, acute hypobaric hypoxia decreases basal prolactin levels.158

Impaired prolactin response to insulin-induced hypoglycemia is associated with more severe oxygen desaturation in obese women without obstructive apneas but with nocturnal hypoxemia.159 Oxygen breathing increases serum concentrations of prolactin in male athletes.160 CPAP treatment has no effect161 or may decrease serum prolactin levels in patients with OSAS.100 Furthermore, hypoxic male patients with stable COPD appear to have normal basal prolactin levels.101,162

In postmenopausal women with respiratory insufficiency, prolactin levels increase following respiratory stimulation with MPA therapy.102 However, prolactin levels were low, near the detection limit throughout the trial. Therefore, the biological significance of observed increase of prolactin during the follow-up has to be interpreted with caution.

**Adrenocorticotropic Axis**

**Corticotropin-Releasing Hormone**

Corticotropin-releasing hormone (CRH), also called corticotropin-releasing factor, is the counter-regulator of GHRH.163 With age, the GHRH/CRH ratio changes in favor to CRH.36 CRH receptors are widely distributed in brain areas involved in the control of breathing.164 CRH acts as a central respiratory stimulant both in healthy men165 and in patients with respiratory failure.166 It increases re-
spiratory rate and tidal volume over a time interval of a few minutes, increases blood oxygen saturation slightly, and decreases end-tidal CO₂. CRH is a part of the hypothalamic-pituitary-adrenal axis and a part of the adaptation mechanisms for stress. In this context, CRH-induced respiratory stimulation is an appropriate response for a fight-or-escape situation.

**Cortisol**

Cortisol has an important role in the maturation process of the lungs, but its possible effects on control of breathing are not known. Cortisol concentrations in the early evening appear to be higher in patients with nocturnal asthma compared to asthma patients without nocturnal symptoms or to healthy control subjects. Acute sleep deprivation leads to an elevation of evening cortisol concentrations. Therefore, the evening rise in cortisol levels is likely to be a stress response reflecting the sleep fragmentation and partial sleep loss of patients with nocturnal asthma.

**Thyroid Hormones**

The importance of thyroid hormones for breathing is demonstrated by the pronounced respiratory changes that accompany conditions with altered thyroid function. Hypothyroidism is characterized by hypoventilation, whereas dyspnea and hyperventilation are signs of hyperthyroidism. The ventilatory responses to hypoxia and hypercapnia decrease in hypothyroidism and increase in hyperthyroidism. The effects of low or high serum levels of triiodothyronine on the respiratory drive are likely to be mediated through parallel changes in metabolic rate. The ventilatory responses normalize as soon as the euthyroid state is reached with treatment.

Hypothyroidism is unlikely to cause sleep apnea, unless other risk factors such as obesity or male gender are present. The low respiratory drive is probably the main reason for the increased prevalence of sleep-disordered breathing in hypothyroidism, although upper airway narrowing due to myxedema or central obesity may also contribute. In hypothyroid patients, inspiratory and expiratory muscle strength correlate inversely with TSH concentrations. Thyroxine-replacement therapy frequently improves hypothyroidism-induced sleep-disordered breathing, but nasal CPAP may be needed especially in obese patients or those with ischemic heart disease.

In OSAS, the decreased serum TSH further decreased on CPAP treatment, the decrease being most pronounced in patients with the most severe nocturnal hypoxemia. However, the response to TRH challenge was normal. In rats, TRH stimulates respiration, the stimulating effect being unrelated to TSH. The mechanism of decreased TSH concentrations in OSAS is not known.

**Catecholamines**

**Epinephrine and Norepinephrine**

Sleep onset is associated with decrease of circulating concentrations of norepinephrine and epinephrine, with a nocturnal nadir occurring approximately 1 h after sleep onset. In contrast, 24-h, daytime, and nocturnal urinary norepinephrine levels as well as both daytime and nocturnal plasma norepinephrine concentrations are increased or within normal limits in patients with OSAS. Norepinephrine concentrations appear to correlate with OSAS severity and SaO₂ during sleep but not during wakefulness. CPAP treatment may decrease serum norepinephrine concentrations in OSAS, whereas epinephrine concentrations may remain unchanged. In one study, there was no change in daytime or nighttime urinary epinephrine or morning plasma epinephrine levels, whereas daytime urinary norepinephrine and morning plasma norepinephrine levels decreased with CPAP treatment. The more severe the nocturnal hypoxemia in OSAS, the more CPAP treatment seems to decrease the concentrations of plasma epinephrine and urinary norepinephrine. In contrast, in noninsulin-dependent diabetic patients with OSAS, fasting epinephrine and norepinephrine levels did not change with CPAP treatment. In summary, most studies report a positive relationship between episodes of obstructive apnea and norepinephrine levels, whereas only a minority of studies report a significant relationship between epinephrine and episodes of obstructive apnea. Contrary to findings in OSAS, positive correlation between plasma norepinephrine concentration and oxygen saturation, expressed as either number of desaturation events, mean SaO₂, or time spent at SaO₂ < 90%, has also been reported.

Epinephrine is also a bronchodilating agent and can modify bronchial hyperreactivity. Norepinephrine has been identified in the carotid bodies, suggesting that it is involved in control of breathing. In dogs, both central and peripheral administration of epinephrine increases respiratory rate and tidal volume. In contrast, central administration of epinephrine may also decrease respiratory rate. In newborn rats, norepinephrine decreases the respiratory rate, and it also decreases ventilation in goats via effects on carotid chemorecep-
Dopamine

Dopamine has an established role in control of breathing. High concentrations of dopamine have been found within the carotid bodies, and it may act as a neurotransmitter in the chemoreception of hypoxemia. This is supported by studies identifying the presence of dopamine receptors within carotid bodies, decrease of ventilation in animals and humans with IV administration of dopamine, and increase of ventilation after administration of dopamine receptor antagonists. Dopamine infusion partially suppresses CO₂ sensitivity, perhaps representing the portion contributed by carotid bodies. IV infusion of dopamine in humans at therapeutic doses results in a small fall in alveolar ventilation and a minimal increase in PaCO₂. However, dopamine infusion may decrease the hyperventilatory response to hypoxia but not to hypercapnia, which strongly suggests that the site of action is in the carotid bodies. Other studies have confirmed these observations. Hypoxia decreases urinary dopamine output both in control subjects and in COPD patients. Moreover, dopamine does not cross the blood-brain barrier, and therefore its ventilatory effects are not likely to be related to central mechanisms.

However, the central action of dopamine cannot be excluded. Dopamine receptors have been found within the CNS, and they may influence the central control of ventilation by some mechanism. Further, inhibition of dopamine in the CNS may also cause sedation, resulting in a modification of ventilatory control.

Other Hormones

Leptin

Leptin is a peptide produced by adipose tissue. Fat mass, the strongest predictor of serum leptin concentration, accounts for > 65% of the variance in leptin levels. In addition to adipose tissue, leptin receptors have been found inter alia in brain, liver, heart, kidneys, lungs, testes, and ovaries in mice. Leptin plays an important role in the regulation of energy balance but has recently also been linked with control of breathing.

Serum leptin levels are higher in women than in men and higher in the luteal than in the follicular phase of the menstrual cycle and increased during pregnancy. However, the association with sex steroids is controversial. Some studies have observed a positive correlation between leptin and progesterone levels, whereas others have found no relationship. Higher leptin levels have been reported before menopause than after menopause, although opposite findings exist. Some studies have found no relationship between menopause and leptin concentrations.

Leptin inhibits neuropeptide Y expression but stimulates CRH release. Since neuropeptide Y inhibits breathing while CRH stimulates it, leptin may thereby influence on respiratory control. In obese mutant mice with leptin deficiency, leptin infusion increased ventilation during wakefulness and sleep, but particularly during rapid eye movement (REM) sleep. The stimulating effect of leptin on ventilation was independent of weight, CO₂ production, and food intake, suggesting a direct effect of leptin on the central respiratory control system. In leptin-deficient mice, hyperventilation of diabetic ketoacidosis was leptin dependent. An increase in HCVR during sleep also indicated the central mechanism of action. Hyperleptinemia is related with hypercapnic respiratory failure. Obese patients have higher fasting serum leptin levels than eucapnic patients. In this study, serum leptin level was a stronger predictor than percentage of body fat for the presence of hypercapnia. Strict dietary restriction in obese subjects produced a depression in respiratory control. Assuming that leptin also stimulates ventilation in humans, an abrupt diet-induced decrease in leptin concentrations may depress ventilation. The concentration of leptin in the cerebrospinal fluid can vary as much as fourfold between individuals. This could explain why some obese subjects are susceptible to hypoventilation and others are not.

Patients with OSAS have hyperleptinemia, which normalizes after treatment with nasal CPAP without weight loss. This suggests that nasal CPAP treatment restores the leptin receptor sensitivity, or that when improving ventilation, less leptin is needed for respiratory stimulation.

Neuropeptide Y

In animals, neuropeptide Y has been linked with respiration. In guinea pig preparations, neuropeptide Y contracted trachea and bronchi but did not have any effect on rat preparations. In dogs, neuropeptide Y-1 receptors mediated a decrease in ventilation and BP, while neuropeptide Y-2 receptors mediated the opposite effect. After central administration, neuropeptide Y decreased respiratory rate.

The role of neuropeptide Y in human control of
breathing is not established, but some data suggest that neuropeptide Y might play a role. In the postmortem examination of 19 patients, those with very high neuropeptide Y levels in the infundibular nucleus had respiratory failure for at least 10 days before death, whereas patients with low levels of neuropeptide Y either died within 2 days of the onset of cardiorespiratory problems or of unrelated causes.223

**Insulin**

Insulin may be involved in control of breathing. In nondiabetic men, fasting insulin and the fasting insulin resistance index correlate inversely with FVC and FEV1.224 Incidence of central sleep apnea appears to be increased in insulin-dependent diabetes mellitus,174 which has been attributed to autonomic neuropathy. The location of insulin receptors in the brainstem and cerebellum suggests that insulin might be involved in control of breathing.69 However, recent observations in diabetic mice with reduced HCVR do not support a direct effect of insulin on ventilatory control.206

**Serotonin**

In rats, serotonin immunoreactive axons decrease with age, suggesting that normal aging may result in a decreased availability of serotonin and decreased facilitation of hypoglossal motoneurons, leading to increased susceptibility to sleep-disordered breathing.225 In cats, serotonin is also a respiratory stimulant226 and a bronchoconstrictor.227 In an animal model, serotonin appears to be important in the maintenance of the patent upper airway in obstructive sleep apnea.228 Serotonin regulates respiratory rhythm by increasing the activity of phrenic motoneurons at the level of the spinal cord.229 In OSAS, serotonin-uptake inhibition increases genioglossal EMG activity,230 with or without improvement in sleep-disordered breathing.230–233

Serotonergic agents may increase central ventilatory drive to pharyngeal muscles, thereby promoting upper airway patency. Fluoxetine,231 buspirone,234 imipramine,235 and paroxetine232 have lead to improvement in some patients but mainly in non-REM sleep.

**Acetylcholine**

In dogs, both central and peripheral administration of acetylcholine increased respiratory rate189, tidal volume decreased initially but increased thereafter. In patients with chronic obstructions, acetylcholine has a stronger bronchoconstrictive property than histamine.236

**Glutamate**

Glutamate acts as an excitatory neurotransmitter in central control of breathing.237 In an animal model, decreased HVR during hypothermia was partly associated with a decrease in glutamate concentration in nucleus tractus solitarius.238

**Histamine**

Histamine is a known bronchoconstrictor.239 In goats, histamine causes an increase of inspiratory neuromuscular drive.240

**Substance P**

In humans, substance P increases ventilation and the HVR.241 Substance P regulates respiratory activity by acting in the CNS and on peripheral sensory receptors.229 In rats, substance P appears to have an antagonistic effect to somatostatin.242 However, the effect may depend on the O2 content of the breathing air. In rats, substance P increases minute ventilation in normoxemia, while after exposure to hypoxia the minute ventilation decreases, suggesting that hypoxia desensitizes substance P receptors.243 In sheep, substance P is a bronchoconstrictor,244 The substance P concentrations in the medulla oblongata were higher in victims of sudden infant death syndrome than in control subjects245 and higher in adult OSAS patients than in control subjects.246 In contrast, another study reported substance P-like immunoreactivity to be lower in infants with risk factors for sudden infant death syndrome.247

**VIP**

In humans, VIP increases ventilation and the HVR, although less than substance P.241 In the cat, VIP is a potent relaxant of airways smooth muscle,248 whereas in human asthmatic and nonasthmatic airways and lungs, VIP concentrations appear not to differ.249 In rat lungs, VIP concentrations decrease with age, but the effects of this phenomenon are not known.250

**GABA**

GABA is an inhibitory neurotransmitter. In animals, GABA decreases ventilation, suggesting that it might be an important neurotransmitter in the central control of breathing.237 However, in healthy humans, GABA appears not to have any role in breathing.251 In snorers with mild sleep-disordered breathing, GABA agonist baclofen increased both REM and non-REM sleep duration but did not change AHI.252
Glycine

Glycine is a central respiratory inhibitor. The glycnergic premotor inhibitory system suppressed hypoglossal motoneuron activity during REM sleep in an animal model, suggesting that glycine may have a role in the regulation of the upper airway patency.

Cholecystokinin

Cholecystokinin, a naturally occurring neuropeptide in the brain, is involved with panic disorder and breathing. In healthy volunteers, cholecystokinin tetrapeptide infusion induced dyspnea, and increased tidal volume and minute ventilation without bronchoconstriction or changes in respiratory rate. The effect on ventilation is not mediated via central CO2-sensitive chemoreceptors. Studies in laboratory rodents suggest that cholecystokinin modulates respiration via cholecystokinin A receptors within medullary or pontine respiratory groups.

SUMMARY

A number of hormones are involved in control of breathing. Progesterone is a well-known respiratory stimulant, whereas the impact of the other reproductive hormones on control of breathing is not established. The role of female hormones is also supported by the distribution of hormone receptors and the increase of sleep-disordered breathing after menopause.

Hypothyroid patients have decreased ventilatory chemosensitivity, which can be improved with thyroxine-replacement therapy. CRH acts as a central respiratory stimulant. Dopamine seems to have an inhibitory action at the level of carotid bodies. Serotonin and serotonergic agents may increase central ventilatory drive to pharyngeal muscles, thereby promoting upper airway patency. Histamine and acetylcholine are bronchoconstrictors whereas epinephrine acts as a bronchodilator.

Improved breathing is linked to increased serum IGF-1 levels in the luteal phase of the menstrual cycle, in pregnancy and in snorers. Somatostatin decreases ventilatory responses and may be involved in pathophysiology of sudden infant death syndrome. Recent evidence suggests that leptin also may influence breathing.

Interactions of hormones and breathing open new perspectives for novel pharmacologic therapies of breathing disorders, and challenge for increasing the research of endocrine aspects of control of breathing in health and disease. With growing body of evidence, hormones seem to have a more important role in regulation of breathing than previously known. Therefore, the concept of “respiratory endocrinology” should perhaps be introduced.

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