A Glandular Problem

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In a recent issue of Respiration, Bottini and Tantucci [1] review some of the endocrine diseases in which sleep apnea syndrome is common. They focus on five conditions: acromegaly, hypothyroidism, diabetes with peripheral neuropathy, Cushing’s disease and syndrome, and hyperandrogenism in which sleep apnea occurs frequently and evidence for sleep disturbance should be sought and if present treated.

Often the predisposition to sleep apnea is a result of anatomical and functional changes in the upper airway caused by the disease [1, 2]. Patients with acromegaly tend to develop airway obstruction because the disease produces mucosal thickening, macroglossia, hypertrophy of the vocal cords, impaired mobility of the cricoarytenoid joints, myopathic changes in the vocal cords, and at times by paralysis of the recurrent laryngeal nerve. Bromocriptine or octreotide treatment may improve the sleep apnea observed in acromegaly but continuous positive airway pressure is more effective.

Narrowing of the upper airway by myxomatous changes in the tissues of the pharyngeal wall and tongue contribute to the obstructive apneas seen in hypothyroidism. In the neuropathy occurring with diabetes, impaired respiratory sensation and/or poor muscle strength may contribute to apneas during sleep [1, 2].

In other cases, the cause of the apneas is still obscure but may involve hormonal effects on the respiratory pattern generator and the response to chemical and mechanical stimulations. Somatostatin, for example, has been reported to inhibit breathing while progesterone, growth hormone, and corticotropin-releasing hormone have been reported to stimulate breathing [2].

Relationships are complex. Hormones affect sleep. For example prolactins seem to stimulate sleep; thus patients with prolactinomas have enhanced slow-wave sleep [3], but corticotropin-releasing hormone may have an arousing action [2].

On the other hand release of hormones like thyrotropin, melatonin, growth hormone, prolactin and cortisol wax and wane with the sleep-wake cycle. Sleep deprivation alters considerably the daily rhythm of release of thyrotropin, growth hormone and prolactin. In patients with sleep apnea, sleeping levels of growth hormone and prolactin are reduced, but continuous positive airway pressure normalizes them [4].

It is now recognized that sleep, respiration and metabolism are closely linked not just by nerve pathways but in addition by a complex network of neurohumoral chemicals that include, in addition to the traditional hormones, cytokines and peptides such as the leptins and hypocretins (also known as orexins) and ghrelin. Some of these substances are produced in both the brain and peripheral tissues [5–9].

Cytokines such as IL-1 and TNF-α increase with sleep deprivation and, when injected into the cerebrospinal fluid of animals, produce sleep [5]. Hypocretins, produced in the lateral hypothalamus, are arousal producing, and abnormalities in hypocretin neurotransmission are
the basis of narcolepsy. They also modulate the production of cytokines and the balance between the Th1 and Th2 cytokines [7, 8]. Leptins produced by adipose tissue seem to exercise a broad influence over sleep metabolism and immune function. Increased levels of leptin are found in patients with obstructive sleep apnea but return to normal with continuous positive airway pressure [9, 10]

Ghrelin is an endogenous ligand of the growth hormone secretagogue receptor and stimulates growth hormone release, increases appetite and causes weight gain. Ghrelin administration in humans also increases slow-wave sleep [6].

All this demonstrates the importance of neurohumoral factors in sleep apnea, but they may even have a greater significance in respiration. One of the basic unanswered questions in respiratory pathophysiology is the mechanism(s) that adjust breathing to changing levels of metabolic rate and levels of arousal. The glands in the broad sense may be a fertile place to look for answers.

References