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EDITORIAL

Modelling pathogenic mechanisms of upper airway dysfunction in the molecular age

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Obstructive sleep apnoea (OSA) is a complex disorder consisting of periods of upper airway obstruction during sleep [1], which are terminated by arousals and oxyhaemoglobin desaturations. Most adults with this disorder present in mid-life with an up to ~20-yr progressive history of loud snoring often of increasing intensity, punctuated by witnessed apnoeas and resuscitative snorts. As sleep apnoea develops, patients may begin to complain of sleep disruption and frank daytime hypersomnolence. The reasons for the development and progression of this disorder, however, are not well understood.

A combination of inherited and acquired factors may contribute to the pathogenesis of OSA [2, 3]. A heritable predisposition to this disorder is suggested by the elevated prevalence of sleep apnoea in males compared with females and in African-American and East Asian compared with Western populations [4–9], as well as by studies demonstrating alterations in pharyngeal anatomy between those with and without sleep apnoea [10–12]. Conversely, weight gain and age can contribute substantially to sleep apnoea prevalence, suggesting that sleep apnoea susceptibility may also be acquired [13, 14]. The precise mechanisms for the development of upper airway dysfunction during sleep, however, are not known.

Investigators have recognised that elevations in upper airway collapsibility play a primary role in the pathogenesis of OSA [15–24]. Recent evidence also suggests that these increases are due to pharyngeal anatomic alterations and disturbances in neuromuscular control, and that both defects in upper airway structures and neuromuscular responses are required for the development of OSA [20, 25]. Upper airway structural defects may develop in association with increases in body weight and age [22, 26–28], whereas aging and post-menopausal status may promote disturbances in pharyngeal neuromuscular control during sleep [29–37]. Thus, pathogenic effects of obesity, age and menopause on upper airway neuromechanical function can combine to increase sleep apnoea susceptibility and progression across the lifespan.

As upper airway obstruction during sleep ensues, changes in pharyngeal mucosal and muscle function can accelerate sleep apnoea progression in humans. SÉRIÈS *et al*. [38] have postulated that disease progression may be related to ultrastructural alterations in pharyngeal tissues, which are characterised by the infiltration of inflammatory cells and remodelling of extracellular matrix tissue. These histopathological changes in the pharyngeal mucosa may deaden sensory receptors that might ordinarily play a critical role in the maintenance of airway patency during sleep [39–42]. Normally, these receptors respond to the markedly negative intraluminal pressures generated during periods of upper airway obstruction by activating pharyngeal dilator muscles that restore airway patency during sleep [43–46]. Mechanical and neurosensory defects related to snoring and sleep apnoea may be exacerbated by the development of epithelial thickening and submucosal oedema [47, 48], which may also degrade the contractile efficiency of pharyngeal dilator muscles [49]. Moreover, obesity and sleep apnoea are associated with excess adipose deposition in pharyngeal tissues [11, 50, 51], which can produce a state of chronic mechanical overload for the pharyngeal musculature [52]. The above findings are consistent with the notion that adiposity leads to a cascade of pharyngeal ultrastructural alterations and progressive defects in upper airway neurosensory and neuromuscular control.

Limited access to human pharyngeal tissue has hampered our ability to dissect histopathological mechanisms of pharyngeal dysfunction during sleep. Human tissue specimens have been acquired from surgery (uvulopalatopharyngoplasty) [52, 53] and/or autopsy. Interpreting histopathological data from these sources is probably confounded by patient selection bias and/or incomplete characterisation of sleep apnoea disease status. Rodent models can overcome these limitations by elucidating the molecular, cellular and histopathological disturbances that result from controlled physiological alterations in normal upper airway tissues.

In the present issue of the *European Respiratory Journal*, ALMENDROS *et al.* [54] have advanced in our understanding of sleep apnoea pathogenesis significantly by utilising an established isolated upper airway model [55–62]. By modelling the impact of repetitive airway closure and reopening on pharyngeal tissue characteristics, these investigators have demon-

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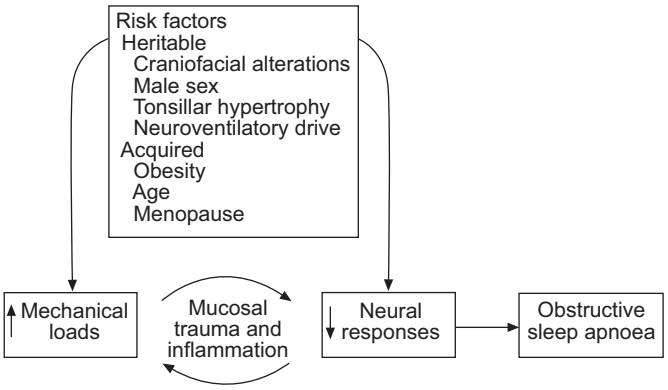

FIGURE 1. Mechanisms of upper airway dysfunction and sleep apnoea pathogenesis. Sleep apnoea risk factors are associated with defects in upper airway mechanical and/or neural control. These alterations produce collapse, vibration (snoring) or repetitive opening and closure of the pharynx (obstructive apnoea). Mechanical trauma can cause inflammation, tissue oedema, and remodelling and sensory disturbances, which further impair pharyngeal mechanics and neural responses, and accelerate the progression toward sleep apnoea.

strated early changes in the expression of inflammatory genes for macrophage inflammatory protein-2, tumour necrosis factor-α, interleukin-1β and P-selectin in the pharyngeal and laryngeal mucosa. Their findings indicate that the mechanical effects of snoring and periods of upper airway obstruction trigger an inflammatory cascade that may ultimately account for the ultrastructural changes in the pharyngeal mucosa, soft tissues, sensory nerves and muscles previously observed in humans [63, 64]. Inflammatory changes in the mucosa may produce sensory impairment [65, 66] and degrade protective reflexes to negative pressure during periods of upper airway obstruction [39–42, 67]. A major implication of the findings of ALMENDROS *et al.* [54] in their rodent model is that a single ''night'' of snoring and/or obstructive apnoeas can initiate the inflammatory changes within the pharyngeal tissues. In humans, it is also possible that upper airway anatomic loads in combination with mechanical trauma can initiate a similar inflammatory process, leading to a series of ultrastructural changes that aggravate neuromechanical defects and accelerate the progression from asymptomatic snoring to OSA (fig. 1).

Some questions also remain about the impact of early changes in the expression of inflammatory genes in the laryngeal and pharyngeal mucosa. What precisely is the stimulus of gene expression changes in both the pharyngeal and laryngeal mucosa? Do these genes lead to infiltration of inflammatory cells and oedema fluid in the pharyngeal mucosa? Are these changes in gene expression responsible for chronic remodelling of the pharyngeal wall? What are the consequences of these histopathological changes on pharyngeal mechanical properties and neuromuscular responses? Is it also possible that ''overspill'' from pharyngeal inflammation contributes to systemic inflammation in obesity and sleep apnoea [68], and mediates the deleterious metabolic and cardiovascular effects observed in obesity and sleep apnoea [69, 70]? While numerous questions still remain, ALMENDROS *et al.* [54] offer a rodent upper airway model to overcome inherent limitations of human studies and elucidate underlying pharyngeal mechanisms of sleep apnoea pathogenesis.

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