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Exploring the cytokine and endocrine involvement in narcolepsy

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Abstract

Narcolepsy is a disabling neurological sleep disorder characterized by excessive daytime sleepiness and abnormal REM sleep manifestations. Recently, the role of cytokines and growth hormone in the regulation of sleep and narcolepsy has been considered, and data suggest that proinflammatory cytokines may be involved in sleep and narcoleptic symptoms. Serum and clinical data were obtained from the Stanford Center for Narcolepsy Research for 39 Narcoleptics (22 Females, 17 Males, age 39 ± 14.9) and 40 controls (13 Females, 27 Males, age 46 ± 17.9). Plasma levels of TNF-α, IL-6, and human growth hormone (hGH) were measured by ELISA. TNF-α and IL-6 were significantly increased in narcoleptic subjects compared to controls ($p = .001$). Interestingly, hGH was significantly increased in narcoleptic subjects ($p < .0001$). There was also a significant difference in the epworth sleepiness scale (ESS) (17.7 ± 4.6 vs. 5.5 ± 3.2, $p < .0001$). These data indicate that narcoleptics, relative to controls, had higher serum levels of TNF-α, IL-6, and hGH. These data suggest that the dysregulation of sleep observed in narcoleptics correlates with the immune and endocrine dysregulation seen in these subjects, and the observed changes may in fact contribute to the higher likelihood of disturbed sleep and/or increased incidence of infection. Additional work is required to fully characterize connections between cytokines and narcoleptic symptomatology.

Keywords: Cytokines; Narcolepsy; Human; Sleep; Immune; Growth hormone

1. Introduction

Narcolepsy is a neurological condition that is characterized by excessive daytime sleepiness and a triad of disassociated REM sleep—cataplexy, hypnagogic hallucinations, and sleep paralysis. Narcolepsy has an HLA association, DQB1*0602, in over 95% of its patients (Mignot et al., 1995; Okun et al., 2002), in addition to a strong association with absent or abnormally low levels of the neuropeptide hypocretin (Mignot et al., 2002; Nishino et al., 2001). These data maintain that this disorder may have an autoimmune origination. However, no evidence has been obtained to confirm this hypothesis. The impact of low or absent hypocretin for narcoleptics may be due to the one of the functions of this neuropeptide. Hypocretin appears to *stabilize*, rather than generate vigilance states (Overeem et al., 2001). This may explain why narcoleptics experience urges to sleep during the day and have pronounced sleep fragmentation at night. With improper hypocretin levels, the narcoleptic is unable to maintain a consistent sleep-wake pattern.

Related to the possibility that narcolepsy may have an autoimmune component is recent work addressing a possible role of cytokines in the regulation of sleep and sleep disorders. Several inflammatory cytokines, including TNF-α and IL-1, have been shown to play a role in the regulation of sleep (Krueger and Majde, 1995; Moldofsky, 1995), while IL-6 has been shown to augment fatigue and sleepiness (Opp and Imeri, 1999). These and other studies linking cytokines to the regulation of sleep and sleepiness have led to speculation that these mediators may play a role in the pathogenesis of narcolepsy, and some studies have suggested that proinflammatory cytokines may be involved in sleep disorders. For example, Vgontzas and colleagues (1997)

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evaluated plasma cytokine levels in patients with obstructive sleep apnea, idiopathic hypersomnia, and narcolepsy. The concentrations of TNFα in plasma were elevated in apneics and narcoleptics compared to controls. Additional studies (Vgontzas et al., 1999, 2002, 2003) have shown elevations and circadian shifts in IL-6 and TNF α, in subjects who are sleep restricted either experimentally or naturally via insomnia. Moreover, although neither IL-1β nor IL-6 was significantly elevated in narcoleptics, IL-6 was markedly elevated in the group of sleep apneics who exhibited obesity (Vgontzas et al., 1997). The relationship between IL-6 and obesity is interesting since narcoleptics tend to be heavier than controls (Dahmen et al., 2001; Hong et al., 2002; Kok et al., 2003; Nishino et al., 2001; Okun et al., 2002). In addition, narcoleptics have been reported to have disturbances in metabolism and food intake as a result of depleted hypocretin (Schuld et al., 2000). These factors may contribute to the elevated obesity levels reported in narcoleptics (Dahmen et al., 2001; Hong et al., 2002; Kok et al., 2003; Nishino et al., 2001; Okun et al., 2002). Interestingly, increased BMI has been related to higher levels of circulating proinflammatory cytokines (Esposito et al., 2003; Vgontzas et al., 1997) and sleepiness (Vgontzas et al., 1998), further suggesting that BMI may be related to proinflammatory cytokines levels and potentially, narcoleptic symptoms. Finally, the possibility that the TNF-α gene is coupled with the development of narcolepsy has been purported by Hohjoh and colleagues (Hohjoh et al., 1999) and is based on the aforementioned work (Vgontzas et al., 1997). They found an increase in the frequency of certain TNF alleles in patients with narcolepsy than in controls. Although not definitive, it leaves open the possibility that certain cytokines may be involved in the development of narcolepsy.

Other researchers have suggested that the observed changes in proinflammatory cytokines seen in sleep disordered patients are not merely the result of impaired T-cell function, but may, in fact, represent a more subtle interaction between immune function and the regulation of sleep patterns. For example, Hinze-Selch et al. (1998) assessed cytokine levels of IL-1β, IL-1ra, IL-2, IL-6 TNF-α, and TNF-β in plasma and in mitogen-stimulated monocytes and lymphocytes in narcoleptics and HLA matched controls. They only found elevated secretion of IL-6 from LPS stimulated monocytes compared to controls. The authors conclude that there are no major T-cell functional abnormalities in narcoleptics, but the elevation in IL-6 may play a role in the REM sleep associated symptoms of narcolepsy since IL-6 promotes the growth of cholinergic neurons (Hinze-Selch et al., 1998).

Animal data strongly implicates a relationship between pro-inflammatory cytokines, particularly IL-1, TNF-α, and IL-6, and sleep modulation (Hogan et al., 2003; Krueger et al., 1998; Krueger and Majde, 2003; Takahashi et al., 1999). Both TNF and IL-1 are known to be somnogenic and have been shown to augment non-rapid eye movement sleep (NREMS) when administered exogenously in rats (Krueger et al., 1998; Krueger et al., 2001; Takahashi et al., 1999). The inclination to extend this theory to humans has not been irrefutably confirmed. Administration of IL-1 or TNF on human sleep reveals species specificity and a dependence on factors such as substance concentration, time, and route of administration, while in animals more consistency in outcomes is observed (Marshall and Born, 2002).

Recent data on IL-6 administration suggest that the sleep modulating properties of IL-6 may only occur during times of illness (Hogan et al., 2003). However, IL-6 does alter NREMS in rats after central administration (Hogan et al., 2003) and in humans after subcutaneous administration (Spath-Schwalbe et al., 1998). Extrapolation of the effects that cytokines have on human sleep has occurred via in vitro measurements, for example serum levels of IL-1β, TNF-α, and IL-6 or cytokine production following lymphocyte stimulation. It must be acknowledged that the most informative animal protocols are prohibited in human research and indirect measurements of the affects of exogenous administration of cytokines in humans in the only means currently available.

The comprehension about human growth hormone (hGH), growth hormone releasing hormone (GHRH) and their role in sleep in both animals and humans in more straightforward (Marshall and Born, 2002). GHRH has been documented to be the best sleep-promoting substance and has been shown to promote NREMS in both animals and humans (Krueger and Majde, 2003; Obal and Krueger, 2001; Steiger, 2003). Few studies have assessed HGH levels in patients with narcolepsy. However, a recent study (Overeem et al., 2003) found that hGH secretion in narcoleptics was dispersed differently than in matched controls over a 24-h period. Refuting expectations, the basal production of hGH was similar in both groups (Overeem et al., 2003). The previous conclusions of these early studies (Besset et al., 1979; Clark et al., 1979) suggest that hGH secretion is blunted in narcolepsy. The methodology of these studies and the time period in which they were conducted imparts skeptical acceptance of the results. One study (Clark et al., 1979) showed hGH concentrations remain stable after administration of L-DOPA. The other two studies (Besset et al., 1979; Higuchi et al., 1979) concentrated on the sleep onset secretion of HGH as their determining factor rather than the entire 24-h period. Knowing that sleep is distributed throughout the 24-h period for narcoleptics, rather than in a concise 8-h period, hGH levels should be altered to some degree from normal subjects due to the alterations in SWS patterns and production.