NEUROENDOCRINOLOGY OF STRESS, INFLAMMATION AND SLEEP

George P Chrousos,
Professor of Pediatrics and Endocrinology, First Dept of Pediatrics and UNESCO Chair on Adolescent Health Care, *National and Kapodistrian University of Athens, Athens, Greece*

Sleep is essential for life in mammals and, us humans, spend approximately one third of our lives sleeping. Sleep and wakefulness are linked to the circadian clock and its *zeitgebers* and function diurnally in succession and mutual opposition of each other. Like other vital systems of the organism, the systems that subserve sleep and wakefulness are both located in the central nervous system (CNS), particularly the hypothalamus and the brainstem. Wakefulness is attained by the Arousal System, ie the Locus Caeruleus (LC) and the reticular formation, which together with the autonomic system and the hypothalamic-pituitary-adrenal (HPA) axis, are also components of the Stress System, that is activated when any stressor exceeds a certain threshold. The need of the organism for sleep is expressed as somnolence (sleepiness, sleep propensity), while the need for tissue rest and recovery from exertion is expressed as fatigue. Somnolence and fatigue are frequently confused with each other, however, they are different feelings subserved by different neural pathways and substrates. Cytokines and adipokines, such as TNF-a and Interleukin (IL)-6, are both somnogenic and fatigogenic, while Stress System mediators, including the key neurotransmitter of the LC and sympathetic system norepinephrine, as well as corticotropin-releasing hormone (CRH) and cortisol, are stimulating wakefulness and arousal. Thus, states associated with hypercytokinemia, such as infections, inflammatory disorders and central obesity, are frequently associated with excessive daytime sleepiness (EDS) and fatigue, while states associated with Stress System activation, such as situational apprehension, anxiety disorders and melancholic depression, are frequently associated with sleep disturbances, including insomnia, early morning awakening, frequent awakenings, etc. We have shown that lack of sleep in normal individuals is associated with elevated circulating somnogenic cytokines, such as IL-6, while stress is associated with elevated CRH, catecholamines and cortisol, all of which promote wakefulness and disturb sleep. We have also shown that patients with central obesity and insulin resistance, or even lean patients with polycystic ovaries and insulin resistance, suffer from sleep apnea, have increased circulating cytokines/adipokines, and suffer from EDS and fatigue. Thus, sleep apnea and EDS and fatigue appear to be components of the Dysmetabolic Syndrome. In contrast, we have shown that patients with idiopathic insomnia have Stress System hyperactivity with elevated CRH, catecholamine and cortisol production throughout the 24h, with the highest difference from normal controls observed in the evening hours. Interestingly, in the same patients, the plasma levels of inflammatory cytokines are also elevated, especially in the evening. In these patients we have the seemingly paradoxical combination of insomnia with fatigue, apparently because both arousal and somnogenic/fatigogenic mediators are elevated. We conclude that sleep disorders share biological markers with stress, inflammatory and metabolic states.