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CYTOKINES, SLEEP AND WAKEFULNESS REGULATION, AND GENERAL HEALTH: A COMMENTARY TO THE REVIEW "THE INFLUENCE OF CYTOKINES ON WAKEFULNESS REGULATION"

Good sleep is crucial for physical and mental health. It is well known that poor sleep quality and excessive daytime sleepiness (EDS) are related to attention disturbances, performance deficits, impaired quality of life, and increased risk of workplace injuries and motor vehicle accidents. Epidemiological studies indicate also that chronic sleep complaints are associated with an increase in adverse health effects and morbidity, caused among others factors by negative effect of disturbed sleep on blood pressure, glucose metabolism, hormonal regulation, and inflammatory processes (Motivala 2011, Mullington et al. 2009).

As patients with severe mental disorders, e.g. schizophrenia, are already at increased risk of premature mortality, mainly due to cardio-vascular diseases (De et al. 2011), and disturbed sleep further increases this risk it is important for every psychiatrist to understand how sleep disturbances are linked not only to mental but also to general health of the patients and how sleep quality and daytime vigilance can be improved.

The importance of research on sleep regulation is further supported by results of recent epidemiological studies. The twelve month prevalence of sleep disorders in European population was found with 7% to be as high as the prevalence of common mental disorders like depression, that was found in 6.9% of investigated subjects (Wittchen et al. 2011). Furthermore, the economic costs of sleep disorders are higher than costs of many severe brain disorders like Parkinson's disease, neuromuscular disorders, multiple sclerosis or epilepsy (Olesen et al. 2012). These data clearly show that sleep complaints are common, have severe negative impact on life quality, mental and general health, and are very cost-consuming. Therefore there is a strong need to search for new solutions to alleviate the burden of sleep disorders.

The review of Weschenfelder at al. in this issue of the Psychiatria Danubina provides a clear and convincing evidence that cytokines and inflammatory processes are an important biological mechanisms leading to EDS, sleep disorders, fatigue, metabolic disorders and unwanted sedative side effects of psychopharmacological treatment. Moreover, their article has several further strengths that should make its lecture stimulating also for readers that are not particularly interested in immune signaling molecules.

Since it is frequently difficult to draw conclusions from the available studies due to the methodological heterogeneity of the applied methods in measuring wakefulness and heterogeneous terms that were used to describe wakefulness, the authors have made an attempt to clarify terms used in vigilance and sleep research. They describe also how these constructs can be measured. Beside mentioning assessment methods that are used in sleep research and sleep medicine, like multiple sleep latency test (MSLT), psychomotor vigilance task (PVT) and continuous performance test (CPT), Epworth, Stanford and Karolinska Sleepiness Scales, the review refers also to the methods for the assessment of wakefulness that are used in EEG research. These methods include spectral analysis of EEG desynchronization, and the alpha attenuation test. Wakefulness, particularly physiological arousal level, can be also estimated through examination of physiological parameters including skin conductance, heart rate variability (HRV) or peripheral arterial tonometry (PAT). This long list of assessments methods of wakefulness, that are mentioned in the article, should be completed with the Maintenance of Wakefulness Test (MWT), that measures the ability to stay awake under soporific conditions for a defined period of time. The MWT can be used as an alternative to MSLT in instances when the volitional ability to stay awake is more important to know than the tendency to fall asleep, that is measured by MSLT (Arand et al. 2005). It is also important to mention a recently developed electroencephalography (EEG)-based algorithm called VIGALL (Vigilance Algorithm Leipzig) (Hegerl et al. 2011). This new technique based on EEG source analysis (Low Resolution Electromagnetic Tomography, LORETA) and EEG activity in different cortical regions attributes to one second EEG segments a certain vigilance stage. It is noteworthy, that VIGALL has been validated by simultaneous EEG/fMRI and EEG/FDG-PET studies, and studies relating vigilance stages to autonomic functions or reaction time and other neuropsychological parameters. Among physiological parameters also pupillometry should be considered as valuable method to assess alertness (McLaren et al. 1992). It was also proposed that in studies evaluating daytime wakefulness and vigilance MWT can be replaced with Oxford sleep resistance (OSLER) test, that is portable and has minimal technical requirements (Krieger et al. 2004).

The use of objective methods for the assessment of wakefulness is very important because rating scales are less sensitive to distinguish EDS from tiredness or fatigue in some patients. Sleepiness and fatigue are two interrelated but distinct phenomena observed in a number of psychiatric, medical and primary sleep disorders. Although both terms are often used interchangeably, they differ in terms of diagnosis and treatment (Shen et al. 2006). Therefore, correct assessment of

sleepiness is one of the most challenging problems in research on wakefulness regulation. On the other hand the assessments of wakefulness based on measures of physiological parameters like heart rate variability, pupillometry, peripheral arterial tonometry, skin conductance, and to less degree on EEG analysis may be influenced by several factors like increased physical or mental activity prior to the examination, smoking or caffeine consumption, anxiety during the test, effects of medication and external factors like temperature, light, noise. Therefore, standardized measurement conditions have to be kept to obtain valid results.

Weschenfelder et al. review also extensively explains the effects of cytokines on biochemistry of wakefulness regulation. From many interesting aspects of this part of their article we would like to stress the link between immune and hypocretin (Hcrt) systems. The discovery of the Hcrt system is regarded as one of the most significant in the basic sleep research and clinical sleep medicine during the past twenty years. Narcolepsy with cataplexy is caused by almost complete loss of Hcrt neurons in the hypothalamus that produce the sleep-wake and REM sleep-regulating Hcrt-1 and Hcrt-2. The low level of Hcrt-1 in the cerebrospinal fluid is used as one of the diagnostic criteria for narcolepsy with cataplexy (Knudsen et al. 2010). The discovery of Hcrt system opens also possibilities for development of new drugs to treat daytime sleepiness (Hcrt system agonists) or insomnia (Hcrt system antagonists).

Although the complexity of cytokine signaling and methodological problems make further research necessary to discover specific treatments methods involving immune mechanisms, current data are already sufficient to make some recommendations for every day clinical psychiatric practice. The accumulating evidence, e.g. in schizophrenia, shows that motivating patients with schizophrenia towards an active lifestyle and toward the cessation of smoking improves not only their immune parameters but also the cardio-metabolic risk profile, negative and cognitive symptoms, and well-being . Furthermore, physical exercise is an important non-pharmacological treatment for sleep disorders. Various studies have verified that physical activity alters the plasma concentration of the many pro-inflammatory cytokines and that cytokines produced during the recovery period after an acute exercise session are very important to promote sleep (Santos et al. 2007). This finding is in agreement with well acknowledged two process model of sleep regulation (Borbely 1982). According to this model sleep is regulated by two processes: the homeostatic process (process S) and the circadian rhythm (process C). The homeostatic need for sleep is dependent, among other factors, from physical activity during the day.

It is noteworthy that in severe mental disorders, e.g. in schizophrenia, physical activity is much lower than in healthy controls, what has been shown in studies that used clinical ratings scales as well as in studies with objective assessment methods like actigraphy (Wichniak et al. 2011). These observations stress the need to monitor and promote physical activity in patients with severe mental disorders.

CONCLUSIONS

Cytokines play an important role in wakefulness regulation. Inflammatory processes may be also an important biological mechanism linking disturbed sleep to cardiovascular disease and increased mortality. The complexity of cytokine signaling and methodological problems cause that the knowledge about effects on cytokines on sleep and wakefulness is still limited, despite the large number of published studies. At present one of the most useful methods to improve sleep and wakefulness, mental and general health of the patients through influence on immune signaling molecules is to motivate the patients towards an active lifestyle and to quit smoking.

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