

## CYTOKINES AND SLEEP – STILL AN UNCLEAR RELATIONSHIP

Wakefulness and sleep-wake-regulation are complex states, a lot of different components and regulatory mechanisms contribute to these functions. One of the factors involved in sleep wake regulation is the immune system, itself being highly complex, consisting of humoral and cellular components. Molecules that transport the information are, beside others, the “immunotransmitters”, the cytokines.

Psychoneuroimmunology – the relationship between psychic processes, neuronal function and the immune system – is a young field of research and related to both, „normal“ psychic function and psychiatric disorders such as major depression or schizophrenia. The evidence for a role of the immune system in sleep and sleep disorders is mainly based on two facts which are well known since many years:

- The sedation and fatigue inducing effect of pro-inflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) or Tumor-necrose-factor-alpha (TNF- $\alpha$ ) is well described by the model of “sickness behaviour” by the group of Robert Dantzer (Dantzer et al. 2008) and
- the extremely strong association between narcolepsy and the HLA-system (Fontana et al. 2010)

Weschenfelder and colleagues wrote for this issue of ‘Psychiatria Danubina’ a comprehensive overview on the current state of knowledge in wakefulness and the definition of different terms and theoretical constructs involved in wakefulness. They describe the heterogeneity of the terminology and the differentiation between subjective and objective categories in sleep wake regulation. The description in part reflects the dilemma of the field: accepted definitions and objective criteria for the different stages are lacking. The current state of knowledge regarding the influence of cytokines on the regulation of wakefulness is modest until today.

While the sleep inducing effect of cytokines was often described, regulatory effects of cytokines on the “normal” sleep wake regulation and on wakefulness are post-hoc conclusions from sickness models. TNF- $\alpha$  and IL-6, key-cytokines of the pro-inflammatory immune-response, are involved in different functions and diseases, e.g. they play a role in sleep apnoea and respond to sleep deprivation (Kapsimalis et al. 2008).

### METHODOLOGICAL CONSIDERATIONS

The vagueness of the topic, the heterogeneity of the components of the immune system (pro- and anti-inflammatory cytokines, different cell types including regulatory cells, components of the innate and the adaptive immune system) and the multiplicity of the functions of the components of the immune system

contribute to the methodological problems which are well addressed by the authors. Interestingly, dependent on the dose and time after injection, the amount of cytokine production and of the time of the day and the route of administration, the same cytokine can have opposite effects (Krueger et al. 2003). Again, TNF- $\alpha$  and IL-6 may be good examples for reliable results because both are stable and can be measured well in the circulating blood while other cytokines such as Interferon-gamma (INF-  $\gamma$ ) or IL-1 are acting primarily in a paracrine way, i.e. in the cell-cell-contact, while serum levels of e.g. IL-1 and INF-  $\gamma$  may not reflect the functional influence of INF- $\gamma$ .

Other methodological issues are the blood brain- and the blood-cerebrospinal-fluid-barriers. Sleep and wakefulness are regulated in the central nervous system as it is outlined by the authors. Most measures of immune components and cytokines in wakefulness, sleep and sleep disorders, however, were performed from serum- or plasma-samples, i.e. from the peripheral immune system. Although there is a communication between CNS and peripheral immune system, different regulatory mechanisms and different concentrations of cytokines play a role in the peripheral and the CNS immune systems. The role of microglia - monocyte derived cells in the CNS – is well addressed by the authors as one of the main carriers of the CNS immune system.

Nevertheless, the CNS has its own immune milieu which is – especially in “normal”, healthy states partly independent regulated from the peripheral immune system, which means that peripheral cytokine levels or cell numbers may not adequately reflect on-going processes during sleep and wakefulness.

### FUTURE DIRECTIONS

The best “objective” measure of sleep and wakefulness are still today neurophysiological, especially electroencephalographic (EEG) data. As the authors mention, studies combining neurophysiological and cytokine data in humans are lacking, although this combination of data would provide better insight into sleep regulation and the role of cytokines, respectively.

Pioneers in the field of the relationship of sleep and immunity are the groups of Krueger et al. (1984) and of Born and colleagues (Besedovsky et al. 2012), but a lot of further research is needed in order to understand the interaction between wakefulness, sleep, the immune system and the neurotransmitters. Combining neurophysiological research methods such as EEG or evoked potentials and / or imaging methods such as functional magnetic resonance tomography (MRT) or positron emission tomography (PET) with the analysis of cytokine levels, cellular immunity and the hypothes-

driven estimation of RNA-levels of cytokines and second messengers might be one future tool to gain new insight into the regulation of sleep and wakefulness.

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