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PHYSIOLOGICAL REVIEW

Tumor necrosis factor alpha in sleep regulation

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SUMMARY

This review details tumor necrosis factor alpha (TNF) biology and its role in sleep, and describes how TNF medications influence sleep/wake activity. Substantial evidence from healthy young animals indicates acute enhancement or inhibition of endogenous brain TNF respectively promotes and inhibits sleep. In contrast, the role of TNF in sleep in most human studies involves pathological conditions associated with chronic elevations of systemic TNF and disrupted sleep. Normalization of TNF levels in such patients improves sleep. A few studies involving normal healthy humans and their TNF levels and sleep are consistent with the animal studies but are necessarily more limited in scope. TNF can act on established sleep regulatory circuits to promote sleep and on the cortex within small networks, such as cortical columns, to induce sleep-like states. TNF affects multiple synaptic functions, e.g., its role in synaptic scaling is firmly established. The TNF-plasticity actions, like its role in sleep, can be local network events suggesting that sleep and plasticity share biochemical regulatory mechanisms and thus may be inseparable from each other. We conclude that TNF is involved in sleep regulation acting within an extensive tightly orchestrated biochemical network to niche-adapt sleep in health and disease.

Introduction

Sleep remains a fundamental scientific enigma. Although significant progress has been made in elucidating roles for sleep in cognition and brain health, the primary functions of sleep have not been firmly established. Moreover, the regulation of sleep and wake is complex and not fully understood, and newer questions have arisen regarding the role and need for local sleep within a specific brain region versus more generalized sleep states. We do, however, appreciate that sleep manifestations are systemic. Sleep affects almost every physiological function, e.g., body temperature, hormone secretions, and respiratory, cardiac, kidney, and immune functions. Sleep actions on the brain range from altering multiple pathologies to recovery from them, as well as performance, mentation, emotion, learning and memory, etc. At the same time, many physiological functions affect sleep, e.g., body temperature, hunger, sexual drive, development, respiration, etc. and extracellular signals involved in the regulation of these functions affect sleep [1]. This latter point is critical to appreciate, as these physiological effects are not accounted for within the two-process (homeostasis and circadian) regulation of sleep model [2]. Fig. 1 illustrates some of the known components of tumor necrosis factor alpha (TNF) regulation and TNF biological activities that are also linked to sleep. Although the biochemical network shown is incomplete, it and the more extensive network (not shown) are likely beyond the capacity of any individual's ability to fully understand the dynamic nuances of such networks. Further, how the components interact with other TNF-regulated processes to orchestrate sleep niche adaptation further challenges comprehension. Herein we focus on only one sleep regulatory substance, TNF. We do so in recognition that other molecules are also involved in sleep regulation, but focus on TNF to illustrate principles of physiological sleep regulation and function. The reader is referred to other reviews for broader treatments of sleep regulation, both biochemical [3–9], neurobiological [10,11], and glialogical [12–15].

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Abbreviations

ADA	adalimumab
CZP	certolizumab pegol
D	Dalton
EEG	electroencephalogram
ERP	evoked response potential
ETA	etanercept
GLM	golimumab
IFX	infliximab
kD	kilo-Dalton
NREMS	non-rapid eye movement sleep
PGRN	progranulin
R	receptor
REMS	rapid eye movement sleep
TH	thalidomide
TNF	tumor necrosis factor alpha

Glossary of Terms

Evoked response potential: the extracellular localized electrical response of the brain to an afferent input. ERPs can also be obtained from co-cultures of cells grown *in vitro* in response to a stimulus.

TNF biology

Within the brain, TNF has many functions including mediation of brain damage, e.g., cerebral ischemia [17], cerebral blood flow, neuro-protection, responses to infection, and synaptic scaling [18]. TNF is expressed by microglia, astrocytes, and neurons [19–22]. The actions of TNF depend not only on the receptor type – either 55 kilo-Daltons (kD) or 75 kD – and adaptor proteins, but also on the context of the stimulus and the interaction with substances that modify TNF activity. In addition, TNF influences whole organism functions such as body temperature [23,24], appetite [25], cognition [26], and brain development [27].

The mechanism of TNF signaling is extensively studied due to its broad influence on physiologic and pathophysiologic processes (Fig. 1) [28–36]. The TNF ligand has two forms, a 26 kD trans-membrane protein [31] and a soluble 17 kD protein. Trans-membrane 26 kD TNF predominates in the brain [37] and fat tissue [38]. In contrast the soluble 17 kD form is, for example, more abundant in muscle and liver [38]. Soluble 17 kD TNF is first transcribed as the trans-membrane 26 kD form, then cleaved by TNF converting enzyme (Fig. 2) to yield the soluble 17 kD TNF form. The regulation of TNF is tissue-specific [39]. Production is driven in part via nuclear factor kappa B and TNF can induce its own expression through this regulatory pathway.

Soluble 17 kD TNF can signal via the trans-membrane TNF receptors (Rs), (Fig. 2, bottom center) as evidenced by the multiple effects induced by injection of soluble 17 kD TNF into the brain including excess sleep. In addition, trans-membrane 26 kD TNF can complex with the soluble TNFRs to induce intracellular pathways within the cell expressing the transmembrane TNF (Fig. 2, left lower panel). The extent of the occurrence of this mechanism in the brain is not known although TNF reverse signaling is described in axonal physiology [40]. Another potential TNF signaling mechanism is direct cell-to-cell contact with the transmembrane TNF binding to the transmembrane R with subsequent intracellular signaling occurring in both cells. Whether this mechanism occurs in brain is unknown (Fig. 2, lower right) although TNF-mediated direct cell-to-cell contact appears to be important in embryonic stem cell differentiation [41].

Cellular responses to TNF signaling can vary broadly based on variability in R expression and adaptor proteins present in the target cell. There are two membrane-bound TNF Rs, a 55 kD R and a 75 kD R. Neither R has intrinsic enzymatic activity, instead signal through recruitment of adaptor proteins. The TNF R super family is divided into two broad categories, according to the adaptor proteins that are recruited upon binding of a ligand [32–36]. Both the 55 kD and 75 kD TNFRs form trimeric complexes with TNF [36]. The specific R type, adaptor protein, and spatial orientation of R-ligand formations dictate target response, which can range from induction of cell death to protection from cell death [32].

The level of expression of TNF in the brain is activity-dependent. When murine facial whiskers are repeatedly

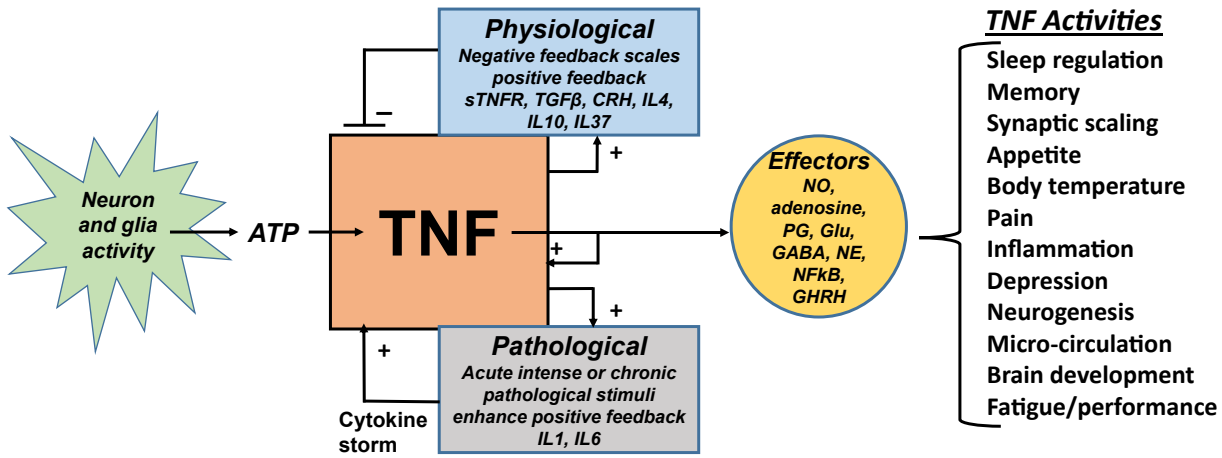

Fig. 1. Tumor necrosis factor α (TNF) regulation in health and disease and its sleep-linked effectors and actions. Physiological regulation of TNF (upper pathway) includes dampening of TNF production via negative feedback. In contrast, pathogenic stimuli can lead to overwhelming positive feedback (lower pathway). TNF can induce its own and other pro-inflammatory cytokines to amplify host-defense reactions to pathological challenges. Clinically this positive feedback can lead to a cytokine storm with the persistence of intense pathological stimuli. Figure abbreviations: CRH, corticotropin-releasing hormone; GABA, gamma-aminobutyric acid; GHRH, growth-hormone-releasing hormone; Glu, glutamic acid; IL, interleukin; NE, norepinephrine; NFkB, nuclear factor kappa B; NO, nitric oxide; PG, prostaglandins; sTNFR, soluble TNF receptor; TGFβ, transforming growth factor β.

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