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Review

Neurobiological mechanisms for the regulation of mammalian sleep–wake behavior: Reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence

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Abstract

At its most basic level, the function of mammalian sleep can be described as a restorative process of the brain and body; recently, however, progressive research has revealed a host of vital functions to which sleep is essential. Although many excellent reviews on sleep behavior have been published, none have incorporated contemporary studies examining the molecular mechanisms that govern the various stages of sleep. Utilizing a holistic approach, this review is focused on the basic mechanisms involved in the transition from wakefulness, initiation of sleep and the subsequent generation of slow-wave sleep and rapid eye movement (REM) sleep. Additionally, using recent molecular studies and experimental evidence that provides a direct link to sleep as a behavior, we have developed a new model, the cellular–molecular–network model, explaining the mechanisms responsible for regulating REM sleep. By analyzing the fundamental neurobiological mechanisms responsible for the generation and maintenance of sleep–wake behavior in mammals, we intend to provide a broader understanding of our present knowledge in the field of sleep research.

Keywords: Wakefulness; Slow-wave sleep; Rapid-eye movement sleep; Mammals; Wake-promoting structures of the brain; Metabolite homeostasis; Molecular mechanisms of sleep; History of identification of sleep stages; Cellular–molecular–network model of REM sleep; Neurotransmitters

Contents

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1. Introduction

Sleep is a highly evolved global behavioral state in the mammalian species. Over the last 50 years, phenomenological and mechanistic aspects of sleep have been studied more carefully and extensively than the waking states. Many philosophers and scientists have behaviorally defined this state in a variety of terms; yet none of those single-state definitions have succeeded in satisfying all aspects of sleep. This failure to define sleep as a single-state lies in the fact that it is not a homogenous state, rather a continuum of a number of mixed states. The different components of this sleep continuum in the mammalian species could broadly be divided into two major states: non-rapid eye movement (NREM) and rapid eye movement (REM). These two states can be identified objectively using behavioral and physiological signs. For the past 50 years, scientists have debated sleep as either an active or passive process of the brain and body. Recent research, however, reveals initiation of NREM sleep is a passive metabolic process of the body and brain but its maintenance is an active process of the brain. Conversely, both initiation and maintenance of REM sleep are active processes of specific neuronal cell groups that form a network located within the caudal midbrain and pons. Although these two sleep states occur in a relatively predictable manner, this predictability could become highly erratic depending on the existing mental and physical state, time, and surrounding space. Utilizing experimental evidence that provides direct link to sleep as a behavior, the aim of this review is focused on the basic mechanisms involved in the transition from wakefulness, initiation of sleep and the subsequent generation of slow-wave sleep (SWS, the latter part of NREM sleep) and REM sleep. Although, in recent years, a number of excellent reviews have been published, most have focused narrowly on findings that support the reviewer's theory. By doing so, majority of those review articles ignored some of the most important findings of the last 20 years, especially to describe the mechanisms of REM sleep. Using a holistic approach, this review/commentary article incorporates those important findings in relation to existing literature and views of many different "Pundits". During the last 20 years, a number of specific functions of sleep have also been discovered, but detailed discussion of those functional advantages and disadvantages of NREM and REM sleep are beyond the scope of this review.