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Review article

Cell adhesion molecules and sleep

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ABSTRACT

Cell adhesion molecules (CAMs) play essential roles in the central nervous system, where some families are involved in synaptic development and function. These synaptic adhesion molecules (SAMs) are involved in the regulation of synaptic plasticity, and the formation of neuronal networks. Recent findings from studies examining the consequences of sleep loss suggest that these molecules are candidates to act in sleep regulation. This review highlights the experimental data that lead to the identification of SAMs as potential sleep regulators, and discusses results supporting that specific SAMs are involved in different aspects of sleep regulation. Further, some potential mechanisms by which SAMs may act to regulate sleep are outlined, and the proposition that these molecules may serve as molecular machinery in the two sleep regulatory processes, the circadian and homeostatic components, is presented. Together, the data argue that SAMs regulate the neuronal plasticity that underlies sleep and wakefulness.

Contents

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1. Introduction

Cell adhesion molecules (CAMs) are proteins found at the surface of the cell membrane that facilitate cell-cell and cell-matrix interactions (Katz et al., 1991). These molecules also mediate interactions between different cell types, both in the central nervous system (CNS) and other organs. Thus, it is not all CAMs that are relevant to CNS function. This review will outline the involvement of CAMs in sleep, but will primarily focus on a specific kind of CAMs located at the synapse, known as synaptic adhesion molecules (SAMs). At some instances, reference to non-synaptic CAMs will also be made, but the focus on SAMs in the context of sleep is due for the most part to their recognized functions in synaptic maturation and plasticity. We will first briefly describe below features and functions of SAMs.

The literature identified roles of SAMs in axonal guidance and synaptogenesis (Akaneya et al., 2010; Biederer et al., 2002; Chen et al., 2010), and this was initially supported by studies that described synapse formation in non-neuronal cells when they were co-cultured with neurons *in vitro* (Scheiffele et al., 2000). SAMs facilitate interactions between neuronal cells as they are generally trans-synaptic partners located on pre- and post-synaptic neurons. These connections facilitate the formation of neuronal circuits and networks that are the basis of neuronal functioning. The literature also describes that SAMs are importantly involved in synaptic maturation and plasticity (Chavis and Westbrook, 2001; Lim et al., 2008; Varoqueaux et al., 2006; Peixoto et al., 2012; Fu et al., 2011; Lin et al., 2003). Indeed, SAMs have been shown to regulate both Hebbian/synaptic plasticity and non-Hebbian/homeostatic plasticity (Fu et al., 2011; Dahlhaus et al., 2010; Jung et al., 2010), making these molecules particularly relevant in adapting CNS functioning as a function of experience and environment.

There are a number of different classes of SAMs, and the five major families are the Immunoglobulins, Cadherins (and Protocadherins), Integrins, Neurexins and Neuroligins, and Ephrins and Eph receptors. Fig. 1 briefly summarizes some of the main functions of these specific families. An in depth discussion of these functions is beyond the scope of this article, but a number of reviews describing roles of SAMs in CNS functions are available (Yamagata et al., 2003; Dalva et al., 2007). Interestingly, some of these SAMs are submitted to extensive alternative splicing resulting in several different isoforms of a given SAM, which makes the system highly complex, albeit intriguing, since different subtypes play distinct roles at the synapse (Chih et al., 2006).

This review will focus specifically on those SAMs that have been shown to be modified by sleep loss, as well as those proposed as candidate molecules in mechanisms underpinning sleep regulation. More precisely, we will describe experiments that identified alterations in SAM expression following sleep deprivation (SD), as well as the studies in which altered SAM expression impacted sleep variables. Lastly, we will outline hypotheses regarding the origin of their roles in sleep regulation, and make propositions with regards to where the field should go to fully understand contributions of SAMs to sleep regulation.

2. Sleep functions and regulation

Sleep is a well-defined, recurring behavior that is essential for survival. A number of physiological roles for sleep have been hypothesized, including roles in CNS metabolism, neurotransmission and synaptic function, glutamate signaling and intracellular calcium homeostasis, and neuroprotection (Terao et al., 2003; Maret et al., 2007; Mackiewicz et al., 2007; Mongrain et al., 2010; Cirelli and Tononi, 2000). Of particular relevance here, is the proposed role for sleep in synaptic plasticity (Krueger and Obal, 1993; Tononi and Cirelli, 2006; Mackiewicz et al., 2009), since SAMs are importantly involved in synaptic plasticity as indicated above.

	Axonal guidance	Synaptogenesis	Synaptic differentiation	Synaptic maturation	Plasticity	Respond to SD	Affect sleep variables
Cadherins	+	+	+	+	+	+	?
Ephrins / Eph	+	+	+	+	+	+	+
Neurexins / Neuroligins	+	+	+	+	+	+	+
Immunoglobulins	+	+	+	-	+	+	+
Integrins	+	+	-	+	+	+	?

Fig. 1. Matrix compiling a summary of different functions of five specific SAM families as reported in previous review articles (Nikonenko et al., 2003; Rougon and Hobert, 2003; Yamagata et al., 2003; Dalva et al., 2007; Krueger et al., 2012; Xu and Henkemeyer, 2012). The matrix also depicts experimental data showing that sleep deprivation (SD) modifies their expression and that their manipulation affects sleep variables (+, denotes literature supporting association with indicated functions/aspects; –, that literature is not supporting such association; ?, that no data are currently available to support the association).

Sleep is regulated by the interaction of a circadian component and a homeostatic component (Borbély, 1982; Daan et al., 1984). The circadian process originates from a molecular loop, is coordinated by the hypothalamic suprachiasmatic nucleus in mammals, and regulates mainly the timing and distribution of wakefulness and sleep. The homeostatic component regulates sleep need as a function of previous wakefulness and sleep history. It is indexed by markers of sleep intensity measured on the electroencephalogram (EEG). The interaction between the circadian and homeostatic processes determines the duration, quality and consolidation of sleep (Dijk and Czeisler, 1994, 1995). Sleep stages are distinguishable by precise EEG activity patterns, reflecting underlying neuronal firing activity. The EEG is thus impacted by circadian and homeostatic influences (Dijk et al., 1997). For instance, slow wave activity (SWA, EEG activity between 0.75 and 4.5 Hz) is considered a measure of sleep intensity mainly reflecting sleep homeostasis. Some of the data presented in sections below will reveal that this sleep feature is affected by SAMs.

There is literature available describing that the expression of several SAMs is influenced by internal circadian time in the CNS (Storch et al., 2007). However, 'circadian' studies are confounded by the fact that internal circadian time varies at the same time as the distribution of sleep and wakefulness. Accordingly, only specific experimental paradigms can separate the influence of circadian time from that of wakefulness and sleep (Maret et al., 2007). In contrast, the effects of SD, which is used to quantify the homeostatic component of sleep regulation, are mainly independent of the internal circadian time, because tissue sampling is generally performed in two different sleep conditions (*e.g.*, undisturbed sleep and enforced wakefulness) but at the same internal circadian time. Therefore, we will hereafter underline how SD impact SAMs, and we will not address how SAM expression or level may vary with circadian time.