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Research Highlight

Nucleus Accumbens, a new sleep-regulating area through the integration of motivational stimuli

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It happens to all of us, how boring activities could make you feel drowsy, whereas stimulating situations maintain us fully awake. Even if complex circuits involving widespread brain areas and neurotransmitters, and genetic factors as well, control sleep rhythm, little is known about how external emotional factors can affect it. In the present study, Oishi and collaborators[1] address the role of nucleus accumbens (NAc), a structure known for its implication in motivation, emotion and pleasure[2, 3], in sleep and whether NAc could affect its regulation in an appealing context.

The nucleus accumbens comprises a contingent of neurons specifically expressing the post-synaptic A_{2A}-receptor ($A_{2A}R$) subtype making them excitable by adenosine, its natural agonist endowed with powerful sleep-promoting properties[4]. The main objective of the authors was to manipulate specifically these neurons to study their role in the context of sleep modulation in presence of motivating factors. For this purpose, authors combined two complementary methods to activate NAc $A_{2A}R$-expressing neurons by using both optogenetics (for an acute activation) and chemogenetics (for a long-lasting activation) in $A_{2A}R$-cre mice. In both cases, large activation of $A_{2A}R$-expressing neurons in NAc promotes slow wave sleep (SWS) by increasing the number and duration of episodes. However, it is well described that NAc is divided in two main parts, namely the core and shell, each with specific anatomical connections and physiological functions[5]. Thus, authors decided to dissect further the respective contribution to SWS of $A_{2A}R$-expressing neurons present in each NAc subdivision. After optogenetic activation of the core, a similar promotion of SWS was observed, whereas no significant effects were induced when activating $A_{2A}R$-expressing neurons within the shell. Logically, their chemogenetic inactivation suppresses SWS in both physiological and sleep-deprived conditions.

The next question raised by these data is how this contingent of $A_{2A}R$-expressing neurons drives the homeostatic balance of SWS? Thanks to GFP-expressing axons emanating from transducted $A_{2A}R$-expressing neurons in the core, authors observed strong efferent projections to the ventral pallidum (VP), and to a lesser degree to the hypothalamus, tuberomamillary nucleus and ventral tegmental area (VTA), three major waking-promoting areas. Besides, they show by intracellular recordings in brain slices that the optogenetic activation of ChR2-expressing axons induced a strong GABA-mediated inhibition of VP neurons. Functionally strengthening these *ex-vivo* data, they show elegantly that a similar optogenetic activation done in freely-moving $A_{2A}R$-cre mice is sufficient to reproduce the SWS promotion observed when activating $A_{2A}R$-expressing core neurons themselves (see above). Finally, the chemogenetic activation of VP GABAergic neurons in Gad2-cre mice suppresses SWS. These latter results are somewhat surprising since they suggest that other efferent pathways of $A_{2A}R$-expressing core neurons targeting powerful wake-promoting system as orexin- or histamine-releasing neurons in tuberal and tuberomamillary hypothalamus respectively are not recruited in effects on SWS reported here. It remains that, taken all data together, the authors proposed that the role in sleep played by $A_{2A}R$-expressing neurons within NAc core is mediated by their inhibitory projections to GABAergic VP neurons.

Finally, the authors hypothesized that this pathway involved in sleep might be modulated directly by a motivational context. For addressing this possibility, $A_{2A}R$-cre mice were exposed to positive stimuli (tasty food, female littermates) or neutral (regular feeding). The results showed that in presence of positive stimuli, animals spent likely more time awake. More interestingly, they observed that this SWS suppression is concomitant to an inactivation of $A_{2A}R$-expressing core neurons projecting to VP, suggesting a potential implication of this pathway in SWS regulation by external stimuli.

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It is an interesting article using elegant experimental approaches to study mechanisms that may explain how external factors can affect or modify the homeostatic sleep-waking balance. For future studies, it will be of particular relevance to address how A_{2A}R-expressing core neurons affect this balance in a more global way. For example, in their Supplementary Figure 4 is illustrated an increased number of rapid eye movement (REM) sleep entrance and a higher probability of REM-sleep to waking transitions in response to the activation of A_{2A}R-expressing core neurons. Does it mean that REM sleep and waking are also modified when modulating the firing of these NAc neurons? In the same way, since activating the shell part of NAc has a tendency to increase SWS quantities, it would be of interest to differentiate effects on sleep between the two NAc areas. A very important point for future research will be how to integrate the present data underlying a crucial role of A_{2A}R-expressing core neurons in sleep, with other sleep-promoting neurons located in the anterior hypothalamus, also activated by adenosine through A_{2A}R recruitment. This model was proposed almost 20 years ago to be the only responsible for sleep-promotion and sleep-waking alternance[6, 7].

To explain the potential role of this pathway in arousal in response to motivating stimuli, the authors proposed that during wake, GABAergic VP neurons inhibit cortical interneurons, thus disinhibiting the cerebral cortex. During this state, NAc core A_{2A}R-expressing neurons are not active since local adenosine concentrations are maintained at low level[8]. In a motivational context, VTA is very active with an increased release of dopamine, thus inhibiting NAc core A_{2A}R-expressing neurons, and allowing GABAergic VP neurons to maintain the cortex active. However, along the day, the levels of adenosine increase and cumulate, stimulating NAc core A_{2A}R neurons and favoring sleep at the end of the day. The activation of GABAergic NAc core A_{2A}R neurons will inhibit GABAergic-VP neurons, favoring sleepiness.

As evidenced once again by the present paper, it is clear that factors and mechanisms implicated in sleep regulation and homeostasis are complex and diverse, mutually influencing each other, therefore still deserving for basic research in the next future. Moreover, studying how external stimulating factors affect the state of waking could open new horizons in learning/memory and attentional processes.

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