刘清华组等揭示睡眠调控的全新机制

Liu Qinghua Group Reveals a New Mechanism of Sleep Regulation

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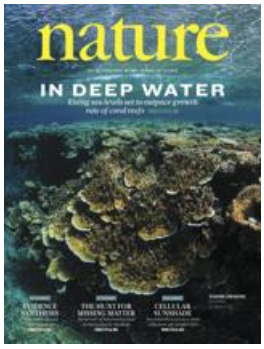
6 月 13 日，《Nature》期刊发表了由日本、中国以及美国合作研究的最新研究——通过定量磷酸化蛋白质组学方法分析了睡眠与脑内蛋白的关系，从而找到 80 种与睡眠相关的磷酸化蛋白质（Sleep-need-index phosphoproteins, SNIPPs），其中 69（86%）个 SNIPPs 和突触有关，后者可以释放信号，传递信息。

文章通讯作者之一、北京生命科学研究所、日本筑波大学国际综合睡眠医学研究所的刘清华教授表示，这是首份揭示“蛋白质磷酸化和睡眠之间”存在关联的研究。

他和团队通过定量磷酸化蛋白质组学方法分析了两种小鼠模型，分别是睡眠剥夺（Sleep deprivation）小鼠和 Sleepy 小鼠。睡眠剥夺小鼠（野生型，Sik3 + / +）和 Sleepy 小鼠[一种 Sik3（AMPK 成员）基因发生显性突变的小鼠，Sik3Slp/+]都具有很高的睡眠需要。研究发现，睡眠剥夺诱导脑蛋白质组的磷酸化累积，其在睡眠中消散。Sleepy 小鼠的脑蛋白质组表现出超磷酸化，类似于睡眠剥夺小鼠大脑中的情况。通过比较确定了 80 个超磷酸化蛋白——称为睡眠需求指数磷酸化蛋白（SNIPPs，sleep-need-index phosphoproteins）。这些睡眠指数蛋白存在于大脑的突触中，这是神经元之间传递信息的间隙。

SNIPPs 蛋白就像是大脑中追踪睡眠的特殊“时钟”，通过磷酸化的累积程度来调节睡眠需求。在健康的小鼠中，SNIPPs 蛋白在觉醒的时间段逐渐累积化学标签——称为磷酸基团（phosphate groups）。这些磷酸基团以相对固定的时间间隔被添加到蛋白质上，帮助追踪小鼠醒来的时间，当积累到一定程度就会转化为相应的睡眠需求，并决定后续睡眠的质量和持续时间。这些蛋白质携带的磷酸酯基团越多，小鼠的睡眠越深和越长。在睡眠期间，磷酸基团被移除并且蛋白质时钟被重置（即发生去磷酸化）。

该项重要成果对于治疗睡眠障碍的新药物的发现具有重要意义，比如，一种能够增加 SNIPPs 蛋白中磷酸基团的药物可能会缓解失眠症。这一发现也可以帮助我们理解为什么有些人只需要很少的睡眠，就能够工作。这可能是因为这些人的睡眠指数蛋白质上添加了更少的磷酸基团，使他们更长时间处于清醒。



Quantitative phosphoproteomic analysis of the molecular substrates of sleep need

睡眠需要的分子底物的定量磷酸化蛋白质组学分析

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Sleep and wake have global effects on brain physiology, from molecular changes and neuronal activities to synaptic plasticity. Sleep–wake homeostasis is maintained by the generation of a sleep need that accumulates during waking and dissipates during sleep. Here we investigate the molecular basis of sleep need using quantitative phosphoproteomic analysis of the sleep-deprived and Sleepy mouse models of increased sleep need. Sleep deprivation induces cumulative phosphorylation of the brain proteome, which dissipates during sleep. Sleepy mice, owing to a gain-of-function mutation in the Sik3 gene, have a constitutively high sleep need despite increased sleep amount. The brain proteome of these mice exhibits hyperphosphorylation, similar to that seen in the brain of sleep-deprived mice. Comparison of the two models identifies 80 mostly synaptic sleep-need-index phosphoproteins (SNIPPs), in which phosphorylation states closely parallel changes of sleep need. SLEEPY, the mutant SIK3 protein, preferentially associates with and phosphorylates SNIPPs. Inhibition of SIK3 activity reduces phosphorylation of SNIPPs and slow wave activity during non-rapid-eye-movement sleep, the best known measurable index of sleep need, in both Sleepy mice and sleep-deprived wild-type mice. Our results suggest that phosphorylation of SNIPPs accumulates and dissipates in relation to sleep need, and therefore SNIPP phosphorylation is a molecular signature of sleep need. Whereas waking encodes memories by potentiating synapses, sleep consolidates memories and restores synaptic homeostasis by globally downscaling excitatory synapses. Thus, the phosphorylation–dephosphorylation cycle of SNIPPs may represent a major regulatory mechanism that underlies both synaptic homeostasis and sleep–wake homeostasis.