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Disturbed Sleep: a novel mechanism discovered in the fruit fly

Prof. Claudia Bagni's team at the Department of Fundamental Neurosciences, UNIL, has identified a novel mechanism contributing to sleep deficits. Sleep is a behavioural and physiological feature frequently affected in individuals with neurodevelopmental disorders. This study might lead to new avenues for the treatment of sleep deficits. This discovery is published on 20th February 2023 in the journal *Nature Communications*.

Sleep is a complex behaviour required for physiological well-being that plays an important role in brain development and cognition. The incidence of sleep disturbance is higher in children with autism spectrum disorder (ASD) compared to typically developing individuals (up to 85%). In addition, sleep disturbances often exacerbate aggression, impulsivity, repetitive behaviours, attention, hyperactivity, anxiety and depression strongly affecting the quality of life of these individuals and their families.
The molecular basis of sleep dysfunctions in neurological diseases remains elusive and understudied. To identify new therapeutic approaches, it is of utmost importance the understanding of the causes and mechanisms of sleep deficits.

For over a century, scientists have been using the fruit fly *Drosophila melanogaster* as model system to explain fundamental biological processes. Of note, nearly 75% of human disease-causing genes have a functional homolog in the fly.

In the research article published on 20th February 2023 in the journal *Nature Communications*, the team, using *Drosophila melanogaster,* identified a molecular mechanism that regulates sleep homeostasis and links a sleep disturbance to metabolic disorders. Recent studies support the notion that sleep and brain metabolism are two interconnected physiological processes fine-tuning each other.

A peek inside the molecular mechanism
The nicotinamide adenine dinucleotide phosphate ($NADP^+$/NADPH) is a molecule required for maintaining cellular redox homeostasis, modulating numerous biological events, including cellular metabolism, neuronal activity and target of proteins involved in circadian rhythm. Prof. Bagni's team has identified a brain regulator of the $NADP^+$/NADPH in brain, namely SREBP.

In this study, they used *Drosophila* with a mutation in a gene, *Cyfip*, which in humans (*CYFIP1*) increases the risk for schizophrenia and autism, both human conditions characterized by sleep deficits. Consistent with sleep disorders in humans, *Drosophila Cyfip* mutants show a reduced sleep time at night, insomnia-like behaviour and a difficulty falling asleep. The team showed that $NADP^+$/NADPH levels are affected in the brains of *Cyfip* mutant flies at the time of the onset of sleep. The researchers analyzed the gene expression profile of *Cyfip* mutant brains and discovered that in this genetic condition, some genes that should be silenced at night – typically expressed during wakefulness – were instead active. Finally, such a dysregulation was caused by the increased activity of SREBP and

one of its molecular targets, the Malic enzyme. SREBP is an important master regulator of lipid synthesis in different organs – including the brain, and here it is associated to a mechanism of sleep regulation in the brain. Importantly, the researchers showed that by reducing SREBP levels, using a genetic and pharmacological approach, *Cyfip Drosophila* mutants recovered the observed sleep deficits.

"We describe for the first time how an impairment in the activity of two important key metabolic regulators, i.e. the sterol regulatory element binding protein SREBP and the Malic enzyme in the brain, contribute to sleep deficits", explains Dr. **Vittoria Mariano,** first author of this study and postdoctoral researcher at the DNF.

A new avenue for therapeutic approaches

Prof. Bagni comments: "*These findings might have an implication for human health because in human, the gene SREBF1 has been associated with chronic insufficient sleep, genome-wide association studies classified human SREBF1 as a risk factor for schizophrenia, and transcription binding sites of genes recognized by SREBP1 are enriched in single nucleotide variants associated to ASD. In addition, alterations in $NADP^+$/NADPH levels are observed in children with ASD*". The molecules and pathways described in *Drosophila* are preserved in mammals, therefore it is tempting to hypothesize that such a discovered mechanism might be conserved in flies and mammals and contribute to a wide range of human neurodevelopmental and neuropsychiatric disorders. Further studies are envisioned by Prof. Bagni's team to validate this mechanism in the mammalian system and in humans.

Links:

Article in *Nature Communications*
Communication in French
Laboratory of Claudia Bagni