Perspective – ultrastructural analyses reflect the effects of sleep and sleep loss on neuronal cell biology

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Abstract

Recent electron microscopic analyses of neurons in the *Drosophila* and rodent brain demonstrate that acute or chronic sleep loss can alter the structures of various organelles, including mitochondria, nucleus, and Golgi apparatus. Here, we discuss these findings in the context of biochemical findings from the sleep deprived brain, to clarify how these morphological changes may relate to altered organelle function. We discuss how, taken together, the available data suggest that sleep loss (particularly chronic sleep loss) disrupts such fundamental cellular processes as transcription, translation, intracellular transport, and metabolism. A better understanding of these effects will have broad implications for understanding the biological importance of sleep, and the relationship of sleep loss to neuropathology.

Key words: sleep; sleep deprivation; organelle; ultrastructure; heterochromatin; Golgi; endoplasmic reticulum (ER); endosomes; lysosomes; reactive oxygen species; unfolded protein response

Sleep loss affects brain function in numerous ways, including disrupting both working and long-term memory, attention, and decision making. While the last two decades have provided new insights into how sleep loss affects neural activity [1–5], gene expression [6, 7], and protein translation [8–11], a complete understanding of the cell biological effects of sleep deprivation (SD) in the brain is still lacking. A recent study by Flores et al. in *Sleep* [12] addresses this question using serial block-face electron microscopy (SBEM) in a *Drosophila* brain structure involved in long-term memory storage. Kenyon cells are intrinsic neurons that integrate a variety of inputs within the mushroom bodies – an associative learning center analogous to the mammalian hippocampus. Previous work has shown that a few hours of brief SD increases spontaneous activity and olfactory responses in Kenyon cells [13]; this is associated with structural changes to Kenyon cells’ synaptic outputs indicating both decreases and...
increases in synaptic strength [14]. Critically, however, longer-duration SD (24 h or more) suppresses Kenyon cell activity and makes sensory responses unreliable [13]. To better understand the intracellular effects of prolonged SD on Kenyon cells, Flores et al. used SBEM to reconstruct their cell bodies and intracellular organelles after ad lib sleep, 11-h SD, and 35-h SD. This study built on previous work from the lab, using single-plane electron microscopy (EM) to resolve these structures in adolescent mouse prefrontal cortex [15]. The results of that work suggested that mitochondrial size and density within pyramidal neurons’ cell bodies was increased by chronic (multiple days) sleep disruption, and to a lesser extent, by acute (a few hours) sleep deprivation (Figure 1). Sleep loss also led to changes in the densities of pyramidal neurons’ lysosomes and early endosomes, suggesting subtle changes to intracellular trafficking [15].

Because the conclusions that can be drawn from single-plane EM are necessarily limited, Flores et al. now use full reconstruction of Kenyon cell bodies in the adult Drosophila brain, using serial block-face scanning electron microscopy (SBEM), to characterize cell structures following either ad lib sleep, 11-h SD, or 35-h SD. The authors quantified changes to organelles in both nucleus and cytoplasm components following SD (Figure 1). Consistent with the lab’s prior findings in mouse neocortex [15], total Kenyon cell cytoplasmic

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**Ultrastuctural and biochemical changes following SD**

- **mitochondria**: mitochondrial size, mitochondrial density, "hourglass" mitochondria (fusion/fission)
- **ROS production**: cytochrome c release, Bax expression
- **cytochrome c oxidase activity**: electron transport chain efficiency
- **lysosomes**: lysosomal density
- **nucleus**: heterochromatin, electron dense clusters, double-strand breaks, histone acetylation, altered transcript profile, altered DNA methylation
- **ER**: ROS production, unfolded protein response (UPR), protein synthesis, altered ribosome-associated mRNAs
- **Golgi apparatus**: Golgi density, altered post-translational modifications
- **endosomes**: endosomal density

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**Figure 1.** Summary of both morphological and biochemical alterations to neuronal organelles following SD. While many organelles such as mitochondria, Golgi, and ER are also present in axons and dendrites, it is unclear how morphology changes in those structures with SD. It is also unclear whether biochemical/functional changes to organelles are cell compartment-specific. Figure was created with BioRender.com.
volume occupied by mitochondria showed a non-significant trend for increasing with increasing-duration sleep loss. The density of Golgi apparatus showed a similar (non-significant) trend, with a tendency for higher Golgi numbers per cell in 35-h SD flies than freely-sleeping flies. More prolonged (i.e. 35-h) SD was also associated with a (non-significant) trend for smaller nuclear volume and nucleus-to-cytoplasm volumetric ratio. Within the nucleus, the authors found statistically significant increases in the absolute number and density of electron-dense "dark clusters" of chromatin following SD of both durations. Among all the measures made by the authors, dark cluster density was the most important parameter for discriminating between Kenyon cells from flies in the three treatment groups.

Here we discuss what these findings could mean, in the context of other recent data, for our understanding of how SD affects the basic cellular biology of neurons in the brain. We also discuss some questions raised by these data that need to be answered in order to understand how SD affects neuronal function.

Effects of Sleep Loss on Neuronal Nuclear Function

The reported increase in dark, roundish nuclear clusters in Kenyon cells suggests possible epigenetic changes to neurons as a function of sleep loss. A similar phenomenon was recently reported using EM – with electron-dense clusters observed in rat hippocampal neurons’ nuclei after chronic (14-day) sleep restriction, with or without caffeine administration [16]. Although the exact driver of cluster formation is still unclear, such clusters likely reflect the same process of heterochromatin formation observed in mammals in the context of both cellular senescence [17] and neuronal plasticity [18]. The increased number and density of heterochromatin clusters after longer-duration SD suggests that long-term sleep loss may disrupt patterns of transcriptionally-active DNA in neurons. Several lines of evidence support this idea (Figure 1). For example, one recent study using an assay for transposable-accessible chromatin with sequencing (ATAC-seq) to identify transcriptionally-accessible regions of DNA showed that SD rapidly (within as little as 3 h) and dramatically changes chromatin accessibility in the mouse cerebral cortex. Surprisingly, however, the vast majority of the differentially accessible DNA sites showed increased, rather than decreased, accessibility after SD [19] – which is more typical of euchromatin. SD may also affect transcription by altering DNA methylation. Studies using methylated DNA immunoprecipitation in rat cortex [20] and 5 mC and 5 hmC arrays in mouse cortex [21] have demonstrated altered methylation patterns after as little as 3-6 h of SD, which are associated with bidirectional changes in gene transcription. SD may also affect histone acetylation, which increases DNA accessibility to transcription factors. Recent findings suggest that both acute and chronic SD increase histone deacetylation activity, reducing levels of histone H3 and H4 acetylation in mouse and rat brain [22–24]. Treating animals with histone deacetylase inhibitors rescued both SD-induced cognitive disruption [22, 24] and late long-term potentiation (LTP) impairments caused by SD [22]. Histone deacetylation could drive the formation of heterochromatin, and thus the formation of electron-dense nuclear clusters reported by Flores et al. and Xie et al. [12, 16].

However, another possibility is that these dark clusters reflect sites of DNA damage, such as those occurring during senescence [17]. It is thought that heterochromatin regulation after DNA damage is important for silencing damaged genes, maintaining genomic stability [25]. Prolonged wake induces double-strand breaks in DNA within Drosophila neurons (Figure 1), and SD can disrupt repair of these breaks [26]. More recent work in zebrafish has shown that sleep facilitates neuronal chromosome rearrangements essential for DNA repair, while SD disrupts these mechanisms [27]. One possibility is that DNA damage accumulation during SD (through generation of reactive oxygen species; ROS [28, 29], or other mechanisms) ultimately leads to neuronal senescence and cell death. Indeed, recent data suggest that neurodegeneration can be triggered in the mammalian brain through this SD-driven mechanism [30].

Thus, a critical unanswered question from the Flores et al. study centers on clarifying the precise nature of these electron-dense nuclear clusters. Understanding how their formation reflects DNA damage, repair, and transcriptional regulation will be essential for understanding how SD affects the most fundamental cell biological processes of neurons – i.e. central dogma (DNA → mRNA → protein) and cell survival.

Sleep Deprivation, Cellular Energetics, and Mitochondrial Function

Mitochondria produce energy for the brain in the form of ATP. This bioenergetic function is regulated by sleep-wake cycles, with higher levels of ATP in wake-active regions of the brain during spontaneous sleep, and ATP reduction during SD [31]. As a byproduct of ATP production, mitochondria generate ROS. Alterations in mitochondrial function could thus couple sleep loss to oxidative stress-mediated DNA damage. Multiple studies across species have found that ROS are generated at higher levels in the brain during prolonged SD [32–34] (Figure 1). This is despite (or perhaps, due to) the fact that prolonged sleep disruption reduces efficiency of the ATP-generating mitochondrial electron transport chain. Critically, this reduction persists in some regions of the brain even after the opportunity for recovery sleep [35]. In turn, generation of ROS in mitochondria is directly coupled to sleep homeostatic responses in sleep regulating neurons in the Drosophila brain [29, 32].

Beyond the effects of SD on mitochondrial energetics, long-term sleep disruption has also been shown to increase Bax expression in mitochondria in the hippocampus, and release of cytochrome c from mitochondria into the cytoplasm [36] (Figure 1). These changes have been linked to both reduced excitability in hippocampal neurons (likely due to reduced ATP [36]) and initiation of neuronal apoptosis and neurodegeneration [37].

Available data suggest that at least in the first hours of sleep loss, neuronal mitochondria respond to this energetic challenge in several ways. Mitochondria in the mammalian neocortex show upregulation of cytochrome c oxidase expression and activity [38–40] and antioxidant responses [33] after 3–12 h of SD (Figure 1). The morphological changes described in Flores et al. after more prolonged SD in flies [12], and described in de Vivo et al. in mice [15], may also be an adaptive response to SD-driven disruption of mitochondrial metabolic function. One
possibility is increasing mitochondrial abundance in neuronal somata is essential for neurons to survive SD-induced disruption of electron transport chain efficiency. This process could be driven by de novo organelle biogenesis [41], mitochondrial transport to the soma from other cellular compartments (i.e., neurites) [42], or increased mitochondrial biogenesis through fusion [43]. The recent report of an increased proportion of “hourglass”-shaped mitochondria after SD in mouse pyramidal neurons [15] (Figure 1) suggests that either mitochondrial fission or fusion may be enhanced by sleep loss. Reported increases in “hourglass”-shaped mitochondria, the presence of “extra-large” mitochondria [15], and a trend toward higher proportion of hyperfused mitochondria [12] after prolonged SD may also reflect the formation of so-called “megamitochondria” through membrane fusion. Megamitochondrial formation likely reflects a process aimed at combating the unfavorable cellular environments and decreasing intracellular ROS level [44] following acute or prolonged SD. While both fission and fusion can be adaptive cellular responses to mitochondrial stress, it is important to note that both are also an essential feature of apoptosis [44, 45].

Other morphological changes to neuronal mitochondria themselves have been reported after prolonged SD – e.g., decreased relative volume of intercrystalline space, which have been reported in both rat hippocampus and neocortex [46]. These intra-organelle morphological changes may relate to SD-driven changes in mitochondrial cristae functions – e.g., changes in cytochrome c storage or electron transport chain activity [46–48]. Taken together, the reported effects of SD on mitochondrial morphology suggest a major impact of sleep loss on neuronal energy production, and potentially also on neuronal viability.

Neuronal proteostasis, and intraneuronal transport – effects of sleep loss on Golgi, endoplasmic reticulum (ER), endosomes, and lysosomes

Flores et al. report a non-significant trend for increased density of Golgi apparatus per Kenyon cell body after longer-duration SD [12]. While de Vivo et al. did not directly measure Golgi or ER, they did report significant increases in pyramidal neurons’ lysosomal size and density with acute and chronic SD, respectively, and reductions in endosomal density with chronic SD [15]. Because the ER, Golgi, lysosomes, and endosomes mediate membrane-associated protein production, trafficking, and quality control, together these ultrastructural findings could reflect SD-induced alterations to intracellular transport and proteostasis.

Across species, biochemical [8, 49–52], transcriptomic [6, 53], and ribosome profiling [8, 11] data suggest that protein translation/quality control and transport are affected by acute sleep loss. For example, in nematodes, Drosophila, and mice [49, 51], a brief period of SD leads to an enhanced unfolded protein response (UPR; the cellular stress response to accumulation of misfolded protein in the ER lumen) (Figure 1). Early SD-induced UPR effects in the brain include suppression of protein translation [9], post-translational modification [54], and increased expression of molecular chaperones [52, 55, 56]. While these changes may aid in normalizing protein quality under conditions of cellular stress, sustained UPR activation engages pro-apoptotic pathways [57, 58], ultimately leading to neurodegeneration.

Disruption of ER function also impacts nuclear function. Critically, another site of potentially DNA-damaging ROS production in neurons is the ER, where ROS are made in the process of chaperone-assisted protein folding [59, 60]. Thus, one possibility is that some of the increased ROS observed in the brain with SD are generated by changes to biochemical processes within the ER (Figure 1).

Changes in Golgi density, lysosomal size and density, and endosome density after SD all suggest that neuronal transport and quality control of membrane-associated protein cargo may change with sleep loss. Critically, however, analysis of these structures within the cell body alone cannot give a complete picture of how sleep loss affects protein synthesis, quality control, and transport. Moreover, to date, there is no data on how sleep loss affects the subcellular distribution of the Golgi, ER, lysosomes, or endosomes in neurons. Appropriate subcellular localization and organization of these organelles is essential for spatial regulation of both protein and mRNA, which in neurons plays vital roles in neurotransmission, synaptic plasticity, and information storage [8, 61, 62]. Beyond these essential functions, the presence of Golgi and ER in neurites plays additional roles, including local calcium buffering, regulation of synaptic extra-cellular glycoproteins, and lipid biogenesis [63, 64]. A recent study from our lab, using neuronal compartment-specific ribosome profiling, demonstrates that mRNAs translated in these membrane-bound organelles vary dramatically with both prior learning and subsequent sleep or SD [8]. Understanding how sleep and SD affect intraneuronal movement of these organelles and their functions in neurites will be essential to understanding how sleep and sleep loss affect neuronal cell biology.

Future Directions

The findings of Flores et al. provide new insights into how cellular structures are affected by sleep loss in Kenyon cells, which play an essential role in Drosophila cognitive function. As is true with transcriptomic and biochemical responses to sleep loss, available data suggest that these changes may also be conserved in neurons across species. This raises a biologically important question – what do these structural changes indicate with respect to the physiological and metabolic processes occurring within neurons? It will be vital for future studies to explore the relationships between the morphological changes present in neuronal organelles after SD, the biochemical and physiological changes occurring within those organelles, and the neuronal and brain-level functional changes due to sleep disruption. Moreover, studies of how organelle morphology, function, and transport within axonal and dendritic cell compartments are affected by sleep and SD will be vital to clarify how brain states affect the cell biology of these essential neuronal structures. Finally, further work is needed to understand (1) what aspects of sleep and SD control these basic mechanisms and (2) how neuronal cellular changes affect the brain and cognition. Progress on these fronts should yield clues to essential, evolutionarily-conserved, sleep functions.

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References

1. Puentes-Mestril C, et al. Linking network activity to synaptic plasticity during sleep: hypotheses and recent data. Front Neural Circuits. 2017;11:61. doi:10.3389/fncir.2017.00061

2. Puentes-Mestril C, et al. How rhythms of the sleeping brain tune memory and synaptic plasticity. Sleep 2019;42. doi:10.1093/sleep/zss095

3. Vyazovskiy VV, et al. Cortical firing and sleep homeostasis. Neuron. 2009;63(6):685–878. doi:10.1016/j.neuron.2009.08.024

4. Delorme J, et al. Sleep loss drives acetylcholine- and somatostatin interneuron-mediated gating of hippocampal activity, to inhibit memory consolidation. Proc Natl Acad Sci USA. 2021;118(32):e201935118. doi:10.1073/pnas.201935118

5. Niethard N, et al. Sleep-stage-specific regulation of cortical excitation and inhibition. Curr Biol. 2016;26(20):2739–2749. doi:10.1016/j.cub.2016.08.035

6. Mackiewicz M, et al. Macromolecule biosynthesis - a key function of sleep. Physiol Genomics. 2007;31(3):441–457.

7. Cirelli C, et al. Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron. 2004;41(1):35–43. doi:10.1016/s0896-6273(03)00814-6

8. Delorme J, et al. Hippocampal neurons’ cytosolic and membrane-bound ribosomal transcript profiles are differentially regulated by learning and subsequent sleep. Proc Natl Acad Sci USA. 2021;118(48):e2018534118.

9. Tudor JC, et al. Sleep deprivation impairs memory by attenuating mTORC1-dependent protein synthesis. Sci Signal. 2016;9(425):ra41. doi:10.1126/scisignal.aad4949

10. Noya SB, et al. The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep. Science. 2019;366(6462):eaay2642.

11. Lyons LC, et al. Translational changes induced by acute sleep deprivation uncovered by TRAP-Seq. Mol Brain. 2020;13(1):165. doi:10.1186/s13041-020-00702-5

12. Flores CC, et al. Identification of ultrastructural signatures of sleep and wake in the fly brain. Sleep. 2021;zbab235. doi:10.1093/sleep/zbab235

13. Bushey D, et al. Sleep- and wake-dependent changes in neuronal activity and reactivity demonstrated in fly neurons using in vivo calcium imaging. Proc Natl Acad Sci USA. 2015;112(15):4785–4790. doi:10.1073/pnas.1419603112

14. Weiss JT, et al. Sleep deprivation results in diverse patterns of synaptic scaling across the Drosophila mushroom bodies. Curr Biol. 2021;31(15):3248–3261.e3. doi:10.1016/j.cub.2021.05.018

15. de Vivo L, et al. Loss of sleep affects the ultrastructure of pyramidal neurons in the adolescent mouse frontal cortex. Sleep. 2016;39(4):861–874. doi:10.5665/sleep.5644

16. Xie G, et al. Caffeine-related effects on cognitive performance: roles of apoptosis in rat hippocampus following sleep deprivation. Biochim Biophys Res Commun. 2021;534:632–638. doi:10.1016/j.bbrc.2020.11.029

17. Penagos-Puig A, et al. Heterochromatin as an Important Driver of Genome Organization. Front Cell Dev Biol. 2020;8:579137. doi:10.3389/fcell.2020.579137

18. Gallegos DA, et al. Chromatin regulation of neuronal maturation and plasticity. Trends Neurosci. 2018;41(5):311–324. doi:10.1016/j.tins.2018.02.009

19. Hor CN, et al. Sleep-wave-driven and circadian contributions to daily rhythms in gene expression and chromatin accessibility in the murine cortex. Proc Natl Acad Sci USA. 2019;116(51):25773–25783. doi:10.1073/pnas.1910590116

20. Ventskovska O, et al. Spontaneous sleep-wake cycle and sleep deprivation differently induce Bdnf1, Bdnf4 and Bdnf9a DNA methylation and transcripts levels in the basal forebrain and frontal cortex in rats. J Sleep Res. 2015;24(2):124–130. doi:10.1111/jsr.12242

21. Massart R, et al. The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes. Transl Psychiatry. 2014;4:e347–e347. doi:10.1038/tp.2013.120

22. Wong LW, et al. Inhibition of histone deacetylase reinitates hippocampus-dependent long-term synaptic plasticity and associative memory in sleep-deprived mice. Cereb Cortex. 2020;30(7):4169–4182. doi:10.1093/cercor/bhaa041

23. Varela RB, et al. Role of epigenetic regulatory enzymes in animal models of mania induced by amphetamine and paradoxical sleep deprivation. Eur J Neurosci. 2021;53(2):649–662. doi:10.1111/ejn.14922

24. Duan R, et al. Histone acetylation regulation in sleep deprivation-induced spatial memory impairment. Neurochem Res. 2016;41(9):2223–2232. doi:10.1007/s11064-016-1937-6

25. Fortuny A, et al. Imaging the response to DNA damage in heterochromatin domains reveals core principles of heterochromatin maintenance. Nat Commun. 2021;12(1):2428. doi:10.1038/s41467-021-22575-5

26. Bellesi M, et al. Contribution of sleep to the repair of neuronal DNA double-strand breaks: evidence from flies and mice. Sci Rep. 2016;6:36804. doi:10.1038/srep36804

27. Zada D, et al. Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. Nat Commun. 2019;10(1):895. doi:10.1038/s41467-019-08806-w

28. Vaccaro A, et al. Sleep loss can cause death through accumulation of reactive oxygen species in the gut. Cell. 2020;181(6):1307–1328.e15. doi:10.1016/j.cell.2020.04.049

29. Hill VM, et al. A bidirectional relationship between sleep and oxidative stress in Drosophila. PLoS Biol. 2018;16(7):e2005206. doi:10.1371/journal.pbio.2005206

30. Zhang J, et al. Extended wakefulness: compromised metabolins in and degeneration of locus ceruleus neurons. J Neurosci. 2014;34(12):4418–4431. doi:10.1523/JNEUROSCI.5025-12.2014

31. Dworak M, et al. Sleep and brain energy levels: ATP changes during sleep. J Neurosci. 2010;30(26):9007–9016. doi:10.1523/JNEUROSCI.1423-10.2010

32. Kempf A, et al. A potassium channel β-subunit couples mitochondrial electron transport to sleep. Nature. 2019;568(7751):230–234. doi:10.1038/s41586-019-1034-5

33. Ramanathan L, et al. Short-term total sleep deprivation in the rat increases antioxidant responses in multiple brain regions without impairing spontaneous alternation behavior. Behav Brain Res. 2010;207(2):305–309. doi:10.1016/j.bbr.2009.10.014

34. Ramanathan L, et al. Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. Neuroreport. 2002;13(11):1387–1390. doi:10.1097/00001756-200208070-00007

35. Andreazza AC, et al. Impairment of the mitochondrial electron transport chain due to sleep deprivation in mice. J Psychiatr Res. 2010;44(12):775–780.

36. Yang RH, et al. Paradoxical sleep deprivation impairs spatial learning and affects membrane excitability and mitochondrial protein in the hippocampus. Brain Res. 2008;1230:224–232.
37. Owen JE, et al. Late-in-life neurodegeneration after chronic sleep loss in young adult mice. Sleep. 2021;44(8):zsab057. doi:10.1093/sleep/zsab057
38. Cirelli C, et al. Differences in gene expression between sleep and waking as revealed by mRNA differential display. Brain Res Mol Brain Res. 1998;56(1-2):293–305.
39. Nikonova EV, et al. Changes in components of energy regulation in mouse cortex with increases in wakefulness. Sleep. 2010;33(7):889–900. doi:10.1093/sleep/s33.7.889
40. Nikonova EV, et al. Differences in activity of cytochrome C oxidase in brain between sleep and wakefulness. Sleep. 2005;28(1):21–27. doi:10.1093/sleep/28.1.21
41. Onyango IG, et al. Regulation of neuron mitochondrial biogenesis and relevance to brain health. Biochim Biophys Acta. 2010;1802(1):228–234.
42. Sheng ZH, et al. Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. Nat Rev Neurosci. 2012;13(2):77–93.
43. Chan DC. Mitochondria: dynamic organelles in disease, aging, and development. Cell. 2006;125(7):1241–1252.
44. Wakabayashi T. Megamitochondria formation - physiology and pathology. J Cell Mol Med. 2002;6(4):497–538.
45. Chan DC. Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev Genet. 2012;46:265–287.
46. Lu Z, et al. Topological reorganizations of mitochondria isolated from rat brain after 72 hours of paradoxical sleep deprivation, revealed by electron cryo-tomography. Am J Physiol Cell Physiol. 2021;321(1):C17–C25.
47. Garcia GC, et al. Mitochondrial morphology provides a mechanism for energy buffering at synapses. Sci Rep. 2019;9(1):18306.
48. Zhao R-S, et al. Mitochondrial electron transport chain, ROS generation and uncoupling (review). Int J Mol Med. 2019;44(1):3–15.
49. Naidoo N, et al. Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. J Neurochem. 2005;92(5):1150–1157.
50. Naidoo N, et al. Aging impairs the unfolded protein response to sleep deprivation and leads to proapoptotic signaling. J Neurosci. 2008;28(26):6539–6548.
51. Sanders J, et al. Distinct unfolded protein responses mitigate or mediate effects of nonlethal deprivation of C. elegans sleep in different tissues. BMC Biol. 2017;15(1):67.
52. Shaw PJ, et al. Correlates of sleep and waking in Drosophila melanogaster. Science. 2000;287(5459):1834–1837.
53. Shaw PJ, et al. Stress response genes protect against lethal effects of sleep deprivation in Drosophila. Nature. 2002;417(6886):287–291.
54. Lee Y, et al. Sleep deprivation impairs learning and memory by decreasing protein O-GlcNAcylation in the brain of adult zebrafish. FASEB J. 2020;34(1):853–864.
55. Naidoo N, et al. A role for the molecular chaperone protein BiP/GRP78 in Drosophila sleep homeostasis. Sleep. 2007;30(5):557–565. doi:10.1093/sleep/30.5.557
56. Brown MK, et al. Aging induced endoplasmic reticulum stress alters sleep and sleep homeostasis. Neurobiol Aging. 2014;35(6):1431–1441.
57. Zinszner H, et al. CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. Genes Dev. 1998;12(7):982–995.
58. Tabas I, et al. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat Cell Biol. 2011;13(3):184–190.
59. Zeeshan HMA, et al. Endoplasmic reticulum stress and associated ROS. Int J Mol Sci. 2016;17(3).
60. Cao SS, et al. Endoplasmic reticulum stress and oxidative stress in cell fate decision and human disease. Antioxid Redox Signal. 2014;21(3):396–413.
61. Donlin-Asp PG, et al. Differential regulation of local mRNA dynamics and translation following long-term potentiation and depression. Proc Natl Acad Sci USA. 2021;118(13):e2017578118.
62. Giandomenico SL, et al. Proteostatic regulation in neuronal compartments. Trends Neurosci. 2022;45(1):41–52.
63. Öztürk Z, et al. Axonal endoplasmic reticulum dynamics and its roles in neurodegeneration. Front Neurosci. 2020;14:48.
64. Govind AP, et al. Activity-dependent Golgi satellite formation in dendrites reshapes the neuronal surface glycoproteome. eLife. 2021;10:e68910.