Sleep disruption, oxidative stress, and aging: New insights from fruit flies

Chiara Cirelli*

Department of Psychiatry, University of Wisconsin, Madison, WI 53719

It is now well established that sleep in the fruit fly *Drosophila melanogaster* shares many key characteristics with mammalian sleep (1, 2) (Fig. 1). As in mammals, sleep in *Drosophila* (i) consists of periods of sustained quiescence associated with an increased arousal threshold; (ii) is modulated by stimulants such as caffeine (2), modafinil (3), and amphetamines (4) and by hypnotics such as antihistamines (2); (iii) is associated with changes in brain activity (5); and (iv) is characterized by changes in the expression of hundreds of genes (6). *Drosophila* sleep, like mammalian sleep, also shows both a circadian and a homeostatic regulation. Flies, like humans, are diurnal animals, and their circadian system is responsible for consolidating most of their sleep during the night (1, 2). The homeostatic system is responsible for the fact that the longer the waking period is, the longer and more intense the subsequent sleep period is (7). In flies, like in mammals, the duration of sleep increases after sleep deprivation, and the amount of sleep recovered depends on prior time awake (8). The intensity of sleep also increases after sleep loss, and sleep becomes less fragmented, i.e., the number of brief awakenings during the night decreases, whereas the duration of each sleep episode increases (8). Like humans, sleep-deprived flies also show reduced vigilance and are less capable of performing certain tasks (8). Sleep in flies, like in mammals, is also more abundant in young flies than in adult flies (2). In a recent issue of PNAS, Koh *et al.* (9) make the important observation that in flies, like in mammals, including humans, sleep also becomes more fragmented with aging. Thus, they demonstrate yet another important similarity between *Drosophila* and mammalian sleep, further establishing fruit flies as a model system for the genetic dissection of sleep mechanisms and functions.

In their study, Koh *et al.* (9) find that aging does not decrease total sleep duration. Moreover, they show that manipulations of ambient temperature that increase or decrease lifespan also decrease and increase sleep fragmentation, respectively, but do not affect total sleep duration or overall levels of locomotor activity. In humans, aging often is associated with both a decrease in total sleep duration and an increase in sleep fragmentation (10). It is not known, however, whether both

Fig. 1. The main features shared between *Drosophila* and mammalian sleep. SD, sleep deprivation. *, ref. 9.

changes have similar effects on the quality of waking, whether one alone is enough to negatively impact waking performance and overall health, or whether their effects are additive. Epidemiological studies have found that changes in sleep duration (both a decrease and an increase) are associated with reduced lifespan (11), but the link between sleep duration and longevity remains a highly controversial issue. Critics argue, for instance, that epidemiological studies can never fully control for comorbidities (reviewed in ref. 12), whereas supporters point out that epidemiological studies tend to control for comorbidities even when they should not (13). Whether sleep fragmentation, with or without changes in sleep duration, can affect lifespan also remains unclear because in most human studies sleep duration is self-reported, and sleep cannot be objectively measured without laboratory

sleep recordings. It is clear, however, that individuals with disturbed sleep (i.e., who reported either difficulties in falling asleep or regular use of hypnotics) have increased risk of cardiovascular disease (14, 15), diabetes (16), and overall mortality (13, 17, 18). A recent study specifically tested only individuals with the same total sleep time (≈ 6.5 h per night) and found that fragmented sleep *per se* is associated with increased levels of lipids, cortisol, and blood pressure (19). Although cause and effect are very difficult to define, the elegant model used by Koh *et al.* (9) should help assign the relative roles of sleep fragmentation and total sleep loss.

Koh *et al.* (9) also find that flies fed throughout life with food containing a low dose of paraquat, a free radical generator, have a reduced lifespan and an increase in sleep fragmentation during the last week of life. The authors speculate that the accumulation of oxidative damage could be one of the mechanisms by which aging affects sleep consolidation. They also suggest that the link between aging and sleep fragmentation may be bidirectional: aging (perhaps via oxidative stress) could cause sleep fragmentation, which, in turn, could further accelerate the aging process. In mammals, several studies have tested whether sleep disruption results in oxidative damage. Rats deprived of sleep for several days show changes in some markers of oxidative stress, such as a decrease in glutathione levels or changes in the activity of antioxidant enzymes (20, 21). The changes were found in some brain regions (e.g., the brainstem) but not in others (e.g., the cerebral cortex). However, the same and other studies have found no evidence, in any brain region, that total sleep deprivation lasting 1–2 weeks is associated with markers of oxidative damage, including protein oxidation, nucleic acid oxidation, and lipid peroxidation (20, 22, 23). Thus, total sleep loss for several days may trigger an oxidative stress response in some brain regions, but the brain seems capable of responding to this stress effectively, thus avoiding the

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*E-mail: ccirelli@wisc.edu.

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oxidative damage. Changes in the activity of antioxidant enzymes, the induction of heat shock proteins and chaperones, and the up-regulation of uncoupling proteins all may represent effective mechanisms by which the brain is protected against oxidative damage. However, whether more long-term changes in sleep quantity and quality,

such as those associated with aging, may ultimately result in oxidative damage is unknown. The possibility of maintaining flies under chronic, lifelong, oxidative stress while assessing their sleep daily will be instrumental in addressing these questions.

In summary, the study by Koh. *et al.* (9) presents a first, promising explora-

tion of the complex relationships between sleep duration, sleep fragmentation, oxidative stress, and aging. In the future, molecular and genetic approaches should be able to move beyond correlative observations and determine whether the link between disrupted sleep and aging is indeed a causal one, and in which direction.

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