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Control of sleep by a network of cell cycle genes

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Sleep is essential for health and cognition, but the molecular and neural mechanisms of sleep regulation are not well understood. We recently reported the identification of TARANIS (TARA) as a sleep-promoting factor that acts in a previously unknown arousal center in *Drosophila*. *tara* mutants exhibit a dose-dependent reduction in sleep amount of up to ~60%. TARA and its mammalian homologs, the Trip-Br (Transcriptional Regulators Interacting with PHD zinc fingers and/or Bromodomains) family of proteins, are primarily known as transcriptional coregulators involved in cell cycle progression, and contain a conserved Cyclin-A (CycA) binding homology domain. We found that *tara* and *CycA* synergistically promote sleep, and CycA levels are reduced in *tara* mutants. Additional data demonstrated that *Cyclin-dependent kinase 1* (*Cdk1*) antagonizes *tara* and *CycA* to promote wakefulness. Moreover, we identified a subset of CycA expressing neurons in the *pars lateralis*, a brain region proposed to be analogous to the mammalian hypothalamus, as an arousal center. In this Extra View article, we report further characterization of *tara* mutants and provide an extended discussion of our findings and future directions within the framework of a working model, in which a network of cell cycle genes, *tara, CycA*, and *Cdk1*, interact in an arousal center to regulate sleep.

Keywords: behavior, Cdk1, cell cycle genes, CycA, *Drosophila*, *pars lateralis*, sleep, TARANIS

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Of all the behaviors required for survival, sleep is one of the most time-consuming, and its loss is linked to many deleterious effects on human health.[1,2] It has been demonstrated that people with disrupted sleep schedules, such as shift workers, have an increased risk of cancer, heart disease and diabetes.[3,4] Sleep deprivation also impairs cognitive and motor functions.[5] Although several theories have been proposed,[6-8] the functions of sleep are not yet clear. Identification of genes and neural circuits that control sleep may facilitate elucidation of sleep function.

The *Drosophila* model for sleep is well suited for discovering sleep regulatory genes through genetic screens. We recently reported the isolation of *taranis* (*tara*) from an unbiased genome-wide forward-genetic screen for short-sleeping mutants.[9] Mutations in *tara* resulted in a reduction of total sleep amount due to fewer and shorter sleep bouts, suggesting that loss of *tara* leads to defects in sleep initiation and maintenance. We found that TARA is expressed widely in neurons and the short-sleeping phenotype of *tara* mutants can be fully rescued with constitutive and ubiquitous expression of *tara*. Importantly, adult-specific pan-neuronal expression of *tara* partially rescued the sleep phenotype, which suggests that TARA has both adult and developmental roles in sleep regulation.

Sleep is controlled mainly by two mechanisms: a circadian mechanism that consolidates sleep to an ecologically relevant time of day and a homeostatic mechanism that ensures an adequate amount of sleep is achieved.[10] We examined the free-running locomotor rhythms of *tara* mutants in constant darkness (DD), and found that most of the severe *tara* mutants were arrhythmic.[9] However, across multiple allelic combinations, the severity of sleep reduction and the degree of arrhythmicity were not highly correlated. Moreover, *tara* mutants exhibited reduced sleep compared with controls in

constant light (LL), which renders both control and mutant flies arrhythmic, demonstrating that the short-sleeping phenotype is not secondary to arrhythmicity. *tara* mutants also exhibited reduced sleep in DD, suggesting that the role of TARA in sleep is independent of light. In both LL and DD, severe *tara* mutants lost over 80% of sleep relative to control flies, which is one of the strongest phenotypes documented among sleep mutants. Together, our data suggest that *tara* regulates sleep amount independently of the circadian mechanism and the light input pathways. These observations leave a defective homeostatic mechanism as the probable cause of reduced sleep in *tara* mutants. In future studies, we will investigate whether and how TARA controls sleep homeostasis.

To further characterize *tara* mutant phenotypes, we examined several additional behaviors. First, we found that *tara* mutants were more likely to wake up in response to brief dim light than control flies (**Fig. 1A**), which suggests that *tara* mutants may be more easily aroused, although it is possible that *tara* mutants are more sensitive to light. Our finding is consistent with previous findings that most short-sleeping flies have lowered arousal threshold,[11] and demonstrate that *tara* mutants can detect dim light. Next, since sleep deprivation can lead to early lethality in flies as well as mammals,[12,13] we measured the lifespan of *tara* mutants. We found that *tara* mutants had a shorter lifespan compared with control flies (**Fig. 1B**), suggesting that reduced sleep in *tara* mutants has consequences for overall fitness, although we cannot rule out the possibility that TARA influences longevity independently of its effect on sleep.[14] Like another short-sleeping mutant, *sleepless* (*sss*),[15] *tara* mutants could not climb as well as control flies (**Fig. 1C**). However, despite their climbing defects, *tara* mutants displayed increased locomotor activity compared with controls, and behaved normally in other behavioral assays. They exhibited neither ether-induced leg shaking nor bang-sensitive paralysis, and performed normally in a taste discrimination assay (**Fig. 1D**). Altogether, our data suggest that while loss of TARA leads to behavioral deficits often associated with reduced sleep, it has little effect on other behaviors.

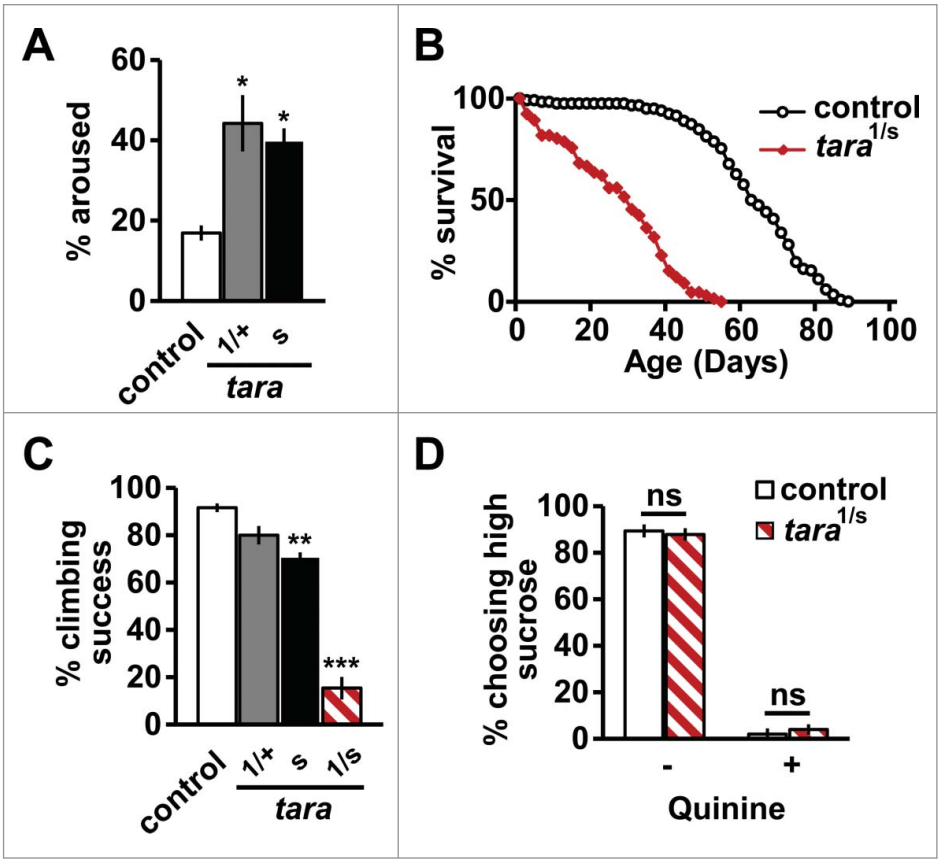

Figure 1. Behavioral phenotypes of *tara* mutants. (**A**) Percentage of control and *tara* flies (n=31–64) that were awakened by a 1 sec pulse of 100 lux light delivered at ZT16. Only flies that were asleep prior to the light pulse are included. (**B**) Survivorship curves of female control and $tara^{1/s132}$ flies (n = 66–118). (**C**) Percentage of control, $tara^{1/+}$, $tara^{s132}$, and $tara^{1/s132}$ flies (n = 37–50) that crossed a 10 cm mark within 10 sec against gravity. (**D**) Percentage of control and $tara^{1/s132}$ flies (n = 46–68) that chose food with 25 mM sucrose, in the absence or presence of 3 mM quinine, over 5 mM sucrose. Control and *tara* flies showed an equivalent preference for a higher concentration of sugar and an equivalent avoidance of bitter tasting quinine. Mean ± SEM is shown. *p < 0.05, **p < 0.01, ***p < 0.001, Chi-square test (A, D), log rank test (B), and one-way ANOVA followed by Dunnett post hoc test relative to control flies (C).

TARA contains a conserved Cyclin-A (CycA) binding homology domain, and *CycA* was previously shown to promote sleep.[16] These observations led us to hypothesize that *tara* interacts with *CycA* to regulate sleep. Using multiple alleles and RNAi-mediated knockdown, we demonstrated that *tara* and *CycA* indeed synergistically interact to promote sleep. Our finding that TARA::GFP fusion protein is enriched in neuronal nuclei [9] is consistent with the previously described role for TARA as a transcriptional co-regulator.[17] However, TARA physically binds CycA and regulates its levels at the post-transcriptional level.[9] Interestingly, the TRIP-Br1 protein, one of the mammalian homologs of TARA, is enriched in the cytoplasm of mammalian cells.[18] Thus, although TARA is expressed mainly in the nucleus, a small pool of TARA may also localize to the cytoplasm. These observations suggest the possibility that TARA regulates sleep through a non-transcriptional mechanism independent of the transcriptional mechanism controlling cell cycle progression.

Although TARA may exert its effect on sleep entirely through post-transcriptional mechanisms, it is possible that at least some of the

effect of TARA on sleep is through transcriptional regulation. TARA and the Trip-Br family of proteins have been shown to act as coregulators of the E2F1-DP1 transcription complex.[19-22] However, we did not find evidence for a genetic interaction between *E2f1* and *tara* for sleep regulation (**Fig. 2**). TARA may partner with different transcription factors depending on the biological context such as sleep regulation versus cell cycle progression.

Cyclins regulate cell cycle progression through their modulation of Cyclin-dependent kinases (Cdks). Previous work showed that CycA can physically interact with Cdk1,[23] which raises the possibility that *Cdk1* may have a role in sleep as well. Indeed our data suggest that CycA regulates sleep through its modulatory action over Cdk1 activity. We found that reduced Cdk1 activity partially rescued the short-sleeping phenotypes of *tara* and *CycA* mutants,[9] suggesting that Cdk1 is a wake-promoting molecule. Since Cdk1 is regulated through inhibitory phosphorylation of its T14 and Y15 residues, we employed a mutant Cdk1-AF (T14A, Y15F) that cannot be inhibited [24] to show that increased activity of Cdk1 suppresses sleep. Given that CycA and Cdk1 are known to physically interact,[23] a direct relationship between CycA and Cdk1 for sleep regulation is likely. Interestingly, we found that both CycA and Cdk1 localize to synaptic regions, which suggests a modulatory role for CycA and Cdk1 over synaptic proteins. Identification of the substrates of the Cdk1 kinase activity relevant for sleep regulation is an important next step we intend to pursue in future experiments.

Recent work in *Drosophila* has demonstrated that knockdown of *Cdk1* significantly reduces seizure duration in both *bang sensitive* (*bas*) and *bang senseless* (*bss*) mutants,[25] which suggests that Cdk1 may modulate ion channel activity and membrane excitability. Several lines of evidence show that ion channels have a dramatic influence over sleep. *Shaker, hyperkinetic, ether-à-go-go, redeye*, and *Rdl* genes, which encode a fast delayed rectifier potassium channel,[26] cytoplasmic β subunit of Shaker,[27] slow delayed rectifier potassium channel,[28] nicotinic acetylcholine receptor,[29] and $GABA_A$ receptor,[30,31] respectively, are all implicated in sleep and may be potential phosphorylation targets of Cdk1.

Previous work showed that CycA protein is expressed in a small number of neuronal clusters including ~14 neurons in the *pars lateralis* (PL),[16] a brain region that together with the *pars intercerebralis* (PI) is thought to be analogous to the mammalian hypothalamus. In order to manipulate the CycA expressing cells, we made use of a Gal4 driver [32] that labels just the dorsal cluster of CycA expressing cells. Activation of these neurons led to strong sleep suppression, suggesting that they serve as an arousal center.[9] Importantly, *tara* knockdown or Cdk1-AF expression, specifically in PL neurons, also suppressed sleep, suggesting that TARA, CycA, and Cdk1 interact in these neurons to control sleep. Given that increased Cdk1 activity in PL neurons phenocopies activation of those neurons, we propose a model in which TARA upregulates CycA levels to inhibit Cdk1, whose kinase activity increases neuronal excitability of wake-promoting PL neurons (**Fig. 3**). Whether Cdk1 activity leads to an overall increase in the excitability of PL neurons is an interesting question for future studies.

How TARA is regulated is another interesting question. We did not observe any changes in TARA levels in circadian pacemaker neurons across the day (**Fig. 4**), but it is possible that TARA levels in PL neurons fluctuate depending on the sleep-wake history. Alternatively, TARA activity rather than its abundance may be under circadian or homeostatic control. Clues to a potential regulator of TARA come from the fact that the PL-Gal4 driver was generated using a fragment of the *corazonin* (*crz*) promoter.[32] Previous studies found that activation of CRZ neurons using a Gal4 driver that contains the full *crz* promoter increases food consumption in starved flies,[33] and that a subpopulation of PL neurons express Gustatory Receptor 43a (GR43a), which functions as a nutrient sensor.[34,35] Although the full *crz* promoter drives expression in a few neuronal groups outside the PL region, it is plausible that PL neurons themselves are involved in the regulation of starvation response. Starved flies sleep less, presumably to forage for food.[36] Moreover, Trip-Br2 is involved in fat metabolism [37]

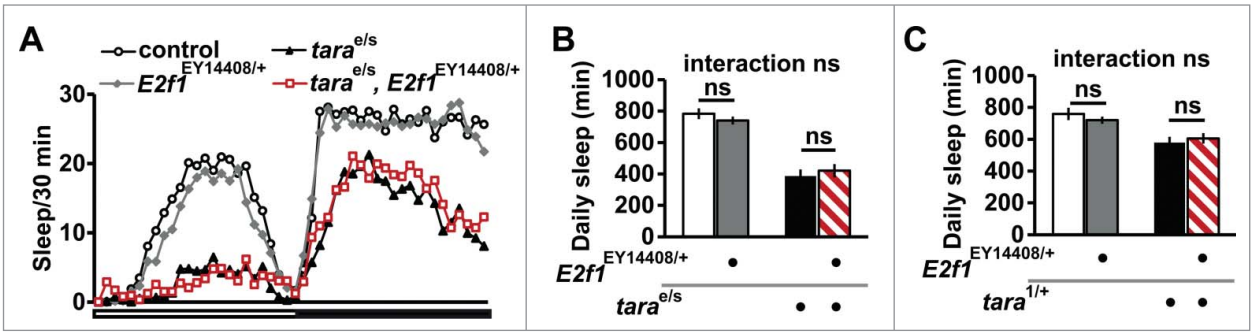

Figure 2. *tara* and *E2f1* appear not to interact for sleep regulation. (**A**) Sleep profile of background control (white circles), $E2f1^{EY14408/+}$ (gray diamonds), $tara^{e01264/s132}$ (black triangles), and $E2f1^{EY14408/+}$, $tara^{e01264/s132}$ (open red squares) female flies (n=17−21) in 30 min bins. The white and black bars below the X-axis represent 12 h light and 12 h dark periods, respectively. (**B**) Total daily sleep amount for the same genotypes indicated in (A). (**C**) Total daily sleep of the indicated genotypes (n = 16 for all genotypes). Mean ± SEM is shown. ns: not significant, 2-way ANOVA followed by Tukey post hoc test (B, C).

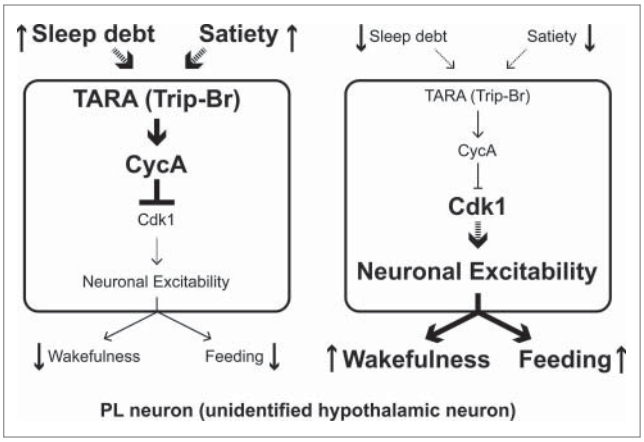

Figure 3. Working model of how TARA promotes sleep. TARA upregulates CycA, which negatively regulates Cdk1 activity in the PL neurons. We propose that increased activity of Cdk1 leads to an increase in the excitability of PL neurons, which promotes wakefulness and feeding. We further speculate that TARA levels and/or activity are modulated by sleep debt and satiety. The two diagrams depict PL neurons when flies have high sleep debt and satiety (left) and when they have low sleep debt and satiety (right), respectively. The mammalian counterparts are indicated in parentheses, and broken lines represent connections that need further investigation.

and Trip-Br1 functions in pancreatic β-cells to regulate insulin secretion.[38] We speculate that TARA functions in PL neurons to coordinately regulate sleep and feeding in response to metabolic as well as sleep-related signals (**Fig. 3**). Interestingly, neurons expressing Diuretic Hormone 44 (DH44) in the PI have been implicated in both the regulation of activity-rest rhythms [39] and the detection and consumption of nutritive sugars,[40] which suggests that multiple neuronal groups may be involved in the coordination of sleep and metabolism. Both PL and PI regions are proposed to be analogous to the mammalian hypothalamus,[41] a major sleep and feeding center.[42,43] It may be that an unidentified subpopulation of the hypothalamic neurons function in a manner analogous to PL neurons to integrate sleep and metabolic signals.

Pan-neuronal knockdown of *tara* had a stronger effect on sleep than *tara* knockdown restricted to PL neurons,[9] which suggests that TARA also acts in other neuronal groups. A number of neuronal populations have been implicated in the regulation of sleep. These include the mushroom body,[44-46] the fan shaped body,[47] the PI,[48] octopaminergic neurons,[48] and the large ventral lateral clock neurons.[30,49] Knockdown of *tara* in these neuronal groups did not result in any significant changes in sleep amount.[9] Further investigation of the anatomical loci of TARA function may reveal additional sleep-relevant neuronal populations.

A number of *Drosophila* sleep factors have been identified in recent years (**Table 1**), but TARA is particularly interesting because it forms a sleep-regulatory gene network with other cell cycle genes, and functions in an arousal center previously unknown for its role in sleep regulation. Interestingly, several studies have shown that cell cycle regulators have additional functions in adult neurons. For instance, *Cyclin E* plays a role in memory formation and synaptic plasticity in mice [50]; knockdown of several Cyclin/Cdk family members rescues the seizure phenotype of *bas* and *bss* mutants in *Drosophila* [25]; and *Cyclin-B1* is upregulated in the hypothalamus of patients afflicted with temporal lobe epilepsy.[51] It is unknown whether Trip-Br proteins regulate sleep and wakefulness in mammals. Further studies of TARA and its mammalian homologs as well as the PL neurons and the neural circuit they participate in may provide valuable insights into the molecular and neural mechanisms of sleep regulation.

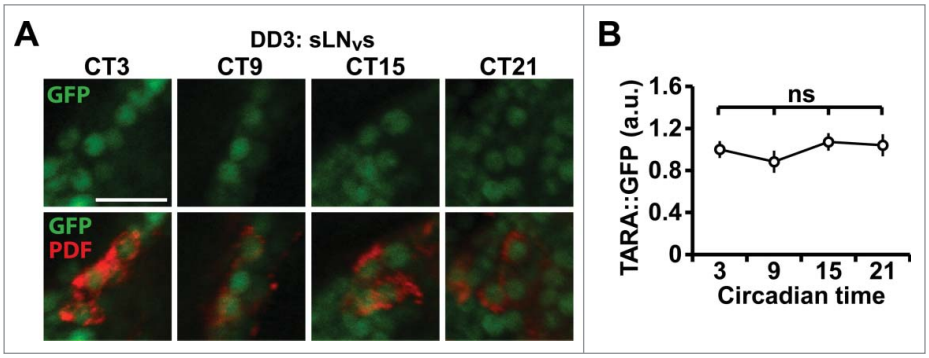

Figure 4. TARA protein levels do not cycle in circadian pacemaker neurons. (**A**) Immunostaining of TARA::GFP in male fly brains on the 3rd day in DD. We used transgenic flies that carry an artificial exon encoding GFP inserted into an intron of *tara* in the genome [52] and therefore are expected to produce endogenous levels of TARA protein fused to GFP. Brains were dissected at indicated circadian times (CT) and stained for GFP (green) and PDF (red), which was used to identify small ventral lateral neurons (sLN_vs), the pacemaker neurons in DD. Scale bar 10μm. (**B**) Quantification of TARA::GFP signal in sLN_vs. Data from 11−16 brain hemispheres are presented. Mean ± SEM is shown. ns: not significant, 2-way ANOVA followed by Tukey post hoc test (B).

Experimental procedures

E2f1^{EY14408} was obtained from the Bloomington Stock Center and outcrossed to a w^- isogenic background (iso31) for 5 generations. Homozygous *E2f1*^{EY14408} are lethal, suggesting that EY14408 is a null or a strong reduction of function allele. All other stocks were described previously.[9] The sleep assay and whole-mount immunostaining of adult brains were performed as previously described.[9] To assess arousability, flies were subjected to a 1 sec pulse of ~100 lux light at Zeitgeber Time (ZT) 16. Only flies that were asleep at the time of light pulse were included in the data analysis, and the proportion of flies that started moving within the next 5 min was determined for each genotype. To determine longevity, *tara*$^{1/s132}$ mutant and control flies were maintained in a 12 hr: 12 hr LD cycle at 25°C throughout their lifespan. Groups of ~30 flies (~15 males and

Table 1. Genes involved in sleep regulation in *Drosophila*.

Protein function	Gene	Reference
Neurotransmission	*Dopamine transporter*	Kume et al., 2005[53]
	Dopamine 1-like receptor 1	Ueno et al., 2012[54]
	5-hydroxytryptamine (serotonin) receptor 1A	Yuan et al., 2006[55]
	Tyramine β hydroxylase	Crocker and Sehgal, 2008[56]
	Tyrosine decarboxylase 2	Crocker and Sehgal, 2008[56]
	Octopamine receptor in mushroom bodies	Crocker et al., 2010[57]
	Resistant to dieldrin (*$GABA_A$ receptor*)	Agosto et al., 2008; Chung et al., 2014[31,58]
	Wide awake	Liu et al., 2014[59]
	GABA transaminase	Maguire et al., 2015[60]
	nicotinic Acetylcholine Receptor α4	Shi et al., 2014[29]
	nicotinic Acetylcholine Receptor α2	Wu et al., 2014[61]
	NMDA receptor 1	Tomita et al., 2015[62]
	Pigment-dispersing factor	Parisky et al., 2008[30]
	Ecdysone receptor	Ishimoto and Kitamoto, 2010[63]
	Sex Peptide	Isaac et al., 2009[64]
	Myoinhibiting peptide precursor	Oh et al., 2014[65]
	Sex peptide receptor	Oh et al., 2014[65]
	short neuropeptide F precursor	Shang et al., 2013[66]
	Diuretic hormone 31	Kunst et al., 2014[67]
	SIFamide	Park et al., 2014[68]
	SIFamide receptor	Park et al., 2014[68]
Ion channel signaling	*Shaker*	Cirelli et al., 2005[26]
	Hyperkinetic	Bushey et al., 2007[69]
	quiver (*sleepless*)	Koh et al., 2008[15]
	Ca^{2+}-channel protein α1 subunit T	Jeong et al., 2015[70]
	Calcineurin B	Nakai et al., 2011; Tomita et al., 2011[71,72]
	Calcineurin A1	Nakai et al., 2011; Tomita et al., 2011[71,72]
	sarah	Nakai et al., 2011[72]
	Sulfonylurea receptor (*ATP-sensitive potassium channel subunit*)	Allebrandt et al., 2013[73]
	Transient receptor potential cation channel A1 ortholog	Roessingh et al., 2015[74]
Cell cycle regulation	*Cyclin A*	Rogulja and Young, 2012[16]
	Regulator of cyclin A1	Rogulja and Young, 2012[16]
	taranis	Afonso et al., 2015[9]
	Cyclin-dependent kinase 1	Afonso et al., 2015[9]
Synaptic development	*Fmr1*	Bushey et al., 2009[75]
	homer	Naidoo et al., 2012[76]
	Neuroligin 4	Li et al., 2013[77]
	Neurexin 1	Larkin et al., 2015[78]
Cellular signaling	*Rolled* (*ERK*)	Foltenyi et al., 2007; Vanderheyden et al., 2013)[79,80]
	Epidermal growth factor receptor	Foltenyi et al., 2007[80]
	spitz	Foltenyi et al., 2007[80]
	Star	Foltenyi et al., 2007[80]
	rhomboid	Foltenyi et al., 2007[80]
	Gold tip	Guo et al., 2011[81]
	Notch	Seugnet et al., 2011[82]
	Delta	Seugnet et al., 2011[82]
	bunched	Seugnet et al., 2011[82]
	basket	Takahama et al., 2012[83]
	foraging	Donlea et al., 2012[84]
	crossveinless c	Donlea et al., 2014[85]
Metabolism	*Insulin-like receptor*	Metaxakis et al., 2014[86]
	Ribosomal protein S6 kinase	Metaxakis et al., 2014[86]
	forkhead box, sub-group O	Metaxakis et al., 2014[86]
	Lipid storage droplet-2	Thimgan et al., 2010[87]
	brummer	Thimgan et al., 2010[87]
	fatty acid binding protein	Gerstner et al., 2011[88]
Circadian	*period*	Hendricks et al., 2000[89]
	cycle	Hendricks et al., 2000; Shaw et al., 2002[12,90]
Immune/stress response	*Heat shock protein 83*	Shaw et al., 2002[12]
	Relish	Williams et al., 2007[91]
	bipolar oocyte (*bip*)	Naidoo et al., 2012[76]

(*Continued on next page*)

Table 1. Genes involved in sleep regulation in *Drosophila*. *(Continued)*

Protein function	Gene	Reference
	Anaplastic lymphoma kinase	Bai and Sehgal, 2015[92]
Protein degradation	*Ubiquitin protein ligase E3A*	Wu et al., 2008[93]
	insomniac	Pfeiffenberger and Allada, 2012; Stavropoulos and Young, 2011[14,94]
Learning and memory	*Cyclic-AMP response element binding protein B*	Hendricks et al., 2001[95]
	dunce	Hendricks et al., 2001[95]
	rutabaga	Hendricks et al., 2001[95]
	Protein kinase, cAMP-dependent, regulatory subunit type 1	Crocker and Sehgal, 2008[56]
	amnesiac	Liu et al., 2008[96]
Other	*Catecholamines up*	Harbison et al., 2009[97]
	Tat interactive protein 60kDa	Pirooznia et al., 2012[98]
	yellow-achaete intergenic RNA	Soshnev et al., 2011[99]
	Activating transcription factor-2	Shimizu et al., 2008[100]
	Adar	Robinson et al., 2016[101]

∼15 females) were collected into food vials within 2 d of eclosion. Males and females were kept together for 2 days, after which they were separated into groups of ∼30 females or males. Flies were transferred to fresh food every 2 days, and the number of dead flies counted. Climbing, leg shaking, bang sensitivity, and taste discrimination assays were performed as described,[15] except that flies had to climb 10 cm within 10 sec to be counted as successful climbers and were allowed to feed for 30 min, and 5 or 25 mM sucrose and 3 mM quinine were used.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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