Neurohormonal and Neuromodulatory Control of Sleep in *Drosophila*

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The fruit fly *Drosophila melanogaster* has emerged in recent years as a tractable system for studying sleep. The sleep-wake dichotomy represents one of the principal transitions in global brain state, and neurohormones and neuromodulators are well known for their ability to change global brain states. Here, we describe studies of two brain systems that regulate sleep in *Drosophila*, the neurohormonal epidermal growth factor receptor system and the neuromodulatory dopaminergic system, each of which acts through a discrete anatomical locus in the dorsal brain. Both control systems display considerable mechanistic similarity to those in mammals, suggesting possible functional homologies.

INTRODUCTION

Sleep is one of the most obvious aspects of physiology and behavior to be regulated by the circadian system. Originally assumed to include only mammals and birds, the circle of sleeping animals has been gradually expanded to include reptiles, amphibians, fish, and eventually invertebrates (Campbell and Tobler 1984; Siegel 1995). Despite many years of study, the fundamental function of sleep remains a mystery. In recent years, the fruit fly *Drosophila melanogaster* has come into its own as a model system for all factors human (with the possible exception of dermatology or dentistry), so it was only a matter of time before it too was tested and shown to exhibit bona fide sleep-like behavior (Hendricks et al. 2000; Shaw et al. 2000; Cirelli 2006).

A phenomenon such as sleep is played out on many levels in the nervous system and thus requires a multi-level analysis. The approach described here aims at manipulating the fly's signal transduction machinery and its neuromodulatory system in order to probe its sleep mechanisms. These studies have revealed requirements for the epidermal growth factor receptor (*Egf-r*)/EGFR-induced extracellular signal-regulated kinase (ERK) signal transduction pathway and for the dopaminergic system as essential elements of the sleep mechanism and have begun to place them in their anatomical context.

THE EGF-R PATHWAY

EGFR signal transduction is one of the classic pathways in development, where it mediates a wide array of cell fate and developmental polarity events in a broad range of organisms (Shilo 2005). The pathway has also been found to be involved in regulating some rhythmic behaviors in hamsters (Kramer et al. 2001), and ectopic overstimulation of the pathway could increase sleep levels in rabbits (Kushikata et al. 1998). Furthermore, ERK,

which is activated by EGFR signaling among many other upstream signaling switches, has been shown to have a role in synaptic plasticity in mammals (Sweatt 2004) as well as in flies (Hoeffer et al. 2003). In the circadian system, ERK signaling is required for normal rhythmicity in *Drosophila* (Williams et al. 2001) and has been implicated in light entrainment in mammals (Coogan and Piggins 2004).

With these findings as background, and with the extensive armamentarium of molecular genetic tools for manipulating *Egf-r* signaling in *Drosophila*, we tested this system's role in sleep by activating and inhibiting upstream components of the pathway. Secretion of *Egf-r* ligands is regulated by the processing proteins Rhomboid and Star (Shilo 2005). Heat shock induction of these gene products was our tool for generating gain-of-function variants, and an RNA interference (RNAi) construct targeted at Rhomboid (Guichard et al. 2002) for generating loss-of-function variants, all under the control of the Gal4-UAS (upstream activating sequence) system (Brand and Perrimon 1993).

MANIPULATION OF THE EGF-R PATHWAY AND SLEEP

When the ligand-processing protein Rhomboid is transiently overexpressed, flies show a pronounced increase in total sleep once they have recovered from the heat shock treatment itself (Fig. 1, top/middle) (Foltényi et al. 2007). When Star as well as Rhomboid is overexpressed, the effect is greater (Fig. 1, bottom), and when the dose of both is doubled (with two doses of the heat shock-Gal4 driver), the effect is further increased (Fig. 1, top/middle). Overexpression of an *Egf-r* ligand, a secreted form of the Spitz (s-Spitz) protein (Schweitzer et al. 1995), similarly increases sleep (Fig. 1, top/middle). An inactive mutant form of Rhomboid, *rho*^{H281Y} (Urban et al. 2002) had no effect other than a short-lived response to the heat shock (Fig. 1, top/middle). Blockade of *Egf-r* responsiveness, using the dominant-negative *Egf-r*^{DN} (Freeman 1996),

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Figure 1. Dose-dependent increase in sleep relative to preheat shock baseline during the night (top) or the day (middle) after overexpression of Rho or Rho and Star, and blockade with *Egfr^{DN1}*. Letters above bars represent statistically significant groups as determined by the Tukey–Kramer HSD test for normally distributed data ($P < 0.05$). (Bottom) Average activity traces of the effect of stimulating EGFR signaling with hs-Gal4 (2 doses) > *rho,Star*. (Gray trace) Preheat shock; (black trace) postheat shock. (Reprinted, with permission, from Foltenyi et al. 2007 [Nature Publishing Group].)

prevented and reversed the increase in sleep due to overexpression of Rhomboid and Star (Fig. 1, top). The increase in total sleep in the affected genotypes was due to an increase in both sleep bout number and bout duration, indicating that flies with up-regulated *Egfr* activity initiated sleep more often and maintained the state longer than normal (Foltenyi et al. 2007). As an indicator of the general health of the flies, locomotor activity during waking bouts was within the range of control genotypes for all strains whose sleep was affected (Foltenyi et al. 2007).

When Rhomboid expression is attenuated throughout the nervous system, flies show a correspondingly pronounced decrease in total sleep (Fig. 2). This was accomplished by driving expression of an RNAi against *rhomboid*, *rho^{DN}*, that was driven by the *elav* panneuronal promoter (Robinow and White 1988). A screen of 48 driver strains with expression in the central nervous system narrowed down the focus of *rho^{DN}* action to a relatively restricted set of cells in the pars intercerebralis that project from the dorsal surface of the protocerebrum down past the esophagus into the tritocerebrum (Fig. 3, left shows one of these, c687). As in the case of overexpression, the number and duration of sleep bouts were affected with an increase in sleep bout number but a dramatic decrease in duration. Once again, their locomotor activity during waking bouts was within the normal range. Circadian rhythms, both period and phase, were also within the wild-type range for these strains (Foltenyi et al. 2007).

To confirm that the pertinent cells in the pars intercerebralis were expressing the *rhomboid* gene product, fly brains expressing a reporter *lacZ* gene under the control of another of the pars intercerebralis drivers, 50Y, were stained with an antibody to the *lacZ* gene product and also counterstained by in situ hybridization with *rho* antisense RNA. The merged image (Fig. 3, right) indicates the presence of the *rhomboid* gene product in the 50Y cells.

Having shown that restricted underexpression of Rhomboid decreases sleep, we wanted to confirm that the heat-shock-induced increase in sleep was at least in part acting through the same cells as the RNAi-induced decrease. To this end, a strain capable of temperature-sensitive activation of the restricted drivers was tested using Gal80^{ts}, a conditional Gal4 repressor, driven ubiquitously by a tubulin promoter (McGuire et al. 2004), and the *Egfr* ligand s-Spitz (cf. Fig. 1). When Gal80 repression of s-Spitz expression in the pars intercerebralis is relieved in adults, the predicted increase in sleep is obtained (Foltenyi et al. 2007).

Finally, to address the question if *Egfr* activation corresponds with the change in behavior, the time course of increased sleep was compared with the time course of molecular changes. When Rhomboid is overexpressed, the increase in its level far outlasts the duration of increased sleep (Fig. 4, top left). In contrast, the time course of activation of the principal intracellular target of *Egfr*, ERK, matches that of the sleep increase very closely (Fig. 4, top right). This was measured using an antibody to the activated (phosphorylated) form of ERK (Foltenyi et al. 2007). Moreover, the principal site of ERK activation after heat shock is in the tritocerebrum (Fig. 4, bottom left), target region for the key cells in the pars intercerebralis (Fig. 3, left).

There is thus a convergence of phenotypes in which molecular effects on ERK activation map both temporally and spatially onto the functional effects on sleep of *Egfr* manipulation. The upshot is that real-time physiological activation or inhibition of the neurohormonal *Egfr* pathway profoundly affects the sleep state of *Drosophila*.

Figure 2. Reduced sleep after directed *rho*-RNAi expression. (Left) Representative traces of sleep levels for one 24-hour light:dark cycle for flies with UAS-*rho*^{DN} (*rho* RNAi) driven by the panneuronal *elav*-Gal4 driver (black trace) and its controls, *elav*-Gal4 (dashed gray trace), and UAS-*rho*^{DN} (solid gray trace). (Right) Histograms for the total nighttime sleep levels for *elav > rho*^{DN}, *50Y > rho*^{DN}, *c687 > rho*^{DN}, and *c687 > rho*^{DN} (error bars represent $\pm$ S.E.M.) and their common control. Letters above bars represent statistically significant groups as determined by the Tukey–Kramer HSD test for normally distributed data ($P < 0.05$). (Reprinted, with permission, from Foltenyi et al. 2007 [Nature Publishing Group].)

THE DOPAMINERGIC SYSTEM IN SLEEP AND AROUSAL

Dopamine is one of several neurotransmitter systems that modulate arousal states in mammals (Robbins et al. 1998; Jones 2005; Monti and Monti 2007). In *Drosophila*, studies of diurnal and sleep-related gene expression have revealed a dopamine receptor and a dopamine catabolizing enzyme, arylalkylamine-*N*-acetyltransferase (Shaw et al. 2000; Cirelli et al. 2005; Zimmerman et al. 2006).

When flies are depleted of dopamine after feeding on 3-iodo-tyrosine (3IY) (Neckameyer 1998), the total amount of time spent sleeping in each 24-hour period increases nearly fourfold (Fig. 5A) (see Andretic et al. 2005). The general health of these flies is unimpaired as measured by the amount of locomotor activity they show during waking epochs. A pharmacological treatment that potentiates dopamine activity, although not as specifically as 3IY inhibits it, produces the opposite effect. Flies fed on methamphetamine sleep less than normal (Fig. 5B) and do not show a normal homeostatic response after sleep deprivation (Fig. 5C).

Genetic manipulations of dopamine levels have comparable effects. A fly mutant for the sleep-regulated enzyme arylalkylamine *N*-acetyltransferase takes an abnormally long time to recover from sleep deprivation, an effect that is dose-dependent (Shaw et al. 2000). A mutant in the fly dopamine transporter gene, *fumin* (Kume et al. 2005), sleeps less than normal and does not show a normal homeostatic response after sleep deprivation. Overexpression of the fly's vascular monoamine transporter protein (VMAT) in its monoaminergic cells produces a heightened level of motor activity (Chang et al. 2006).

Other measures of arousal are also affected by manipulations that modify dopaminergic cells. Methamphetamine substantially increases the courtship ardor of male flies (Andretic et al. 2005). Genetic manipulations of excitability and synaptic release in dopaminergic cells alter the fly's sensitivity to anesthesia: Hyperexcitation decreases sensitivity and blockade of dopamine release increases sensitivity (van Swinderen 2006). The fly's response to the salience of a stimulus is dependent on functional synaptic release from dopaminergic neurons (Andretic et al. 2005; Zhang et al. 2007), a property that is reflected in the defects in associative conditioning seen after blockade of

Figure 3. Confocal images of whole-mount brains, frontal view: (Left) the pars intercerebralis (PI) expression pattern of Gal4-c687 as revealed by a membrane-bound form of green fluorescent protein (GFP) (UAS-mCD8::GFP.L) (green), with the neuropil counterstained by antibody nc82 (red); (right) a close-up of the PI region of a brain expressing LacZ under 50Y control, costained for *rho* with antisense RNA (red), for an antibody to β -galactosidase (green), and with DAPI (blue) to show cell nuclei. Bar, 20 μ m. (Reprinted, with permission, from Foltenyi et al. 2007 [Nature Publishing Group].)

Figure 4. Increased sleep correlated with increased levels of ppERK. (Top left) Immunoblots for time course of heat-shock-induced expression in whole heads using antibodies against ppERK, actin, and Rho. (Top right) Time course of levels of ppERK, normalized to actin loading control in top left, prepared from fly heads. (Bottom left) A whole-mount *hs-Gal4 > rho, Star* brain after heat shock, stained for ppERK (green); (bottom right) its *hs-Gal4 > w¹¹¹⁸* control. (Reprinted, with permission, from Foltényi et al. 2007 [Nature Publishing Group].)

Figure 5. Effects on sleep of manipulating the dopaminergic system. (A) Inhibition of dopamine synthesis by 3-iodotyrosine. (Closed square) Total sleep during successive 24-hour periods; (closed diamond) counts per waking minute during each 24-hour period. Asterisks indicate statistically significant difference from baseline day 0 (*t*-test with Bonferroni correction, $P < 0.05$). (B) Potentiation of dopamine by methamphetamine. (Closed square) 0 mg/ml; (closed diamond) 0.32 mg/ml; (closed circle) 0.64 mg/ml; (closed triangle) 1.25 mg/ml mixed into the food. (C) Methamphetamine effect on rebound after sleep deprivation. Cumulative plot of sleep loss or gain for deprivation (day 1) and recovery (day 2) versus their respective baseline days. (Closed diamond) No treatment; (closed triangle) 9-hour sleep deprivation on day 1; (closed square) 9-hour sleep deprivation on day 1 + 1.25 mg/ml methamphetamine on day 2. Asterisks indicate statistically significant difference after sleep deprivation with (closed square) and without (closed triangle) methamphetamine (*t*-test with Bonferroni correction, $P < 0.05$). (Reprinted, with permission, from Andretic et al. 2005 [© Elsevier].)

Figure 6. Dopaminergic system in the *Drosophila* brain. Whole-mount brain, frontal view, expressing EGFP in dopaminergic cells, driven by the promoter for tyrosine hydroxylase (*Th-Gal4* > UAS-EGFP). Silhouettes of mushroom bodies are shown in black outline.

dopaminergic transmission (Schwaerzel et al. 2003) or dopamine receptor function (Kim et al. 2007).

The focus of all of these dopaminergic effects is likely to be the mushroom bodies, at least in part. Mushroom body output is necessary for the same responses that require dopamine: the salience response (van Swinderen and Greenspan 2003; Zhang et al. 2007) and associative conditioning (Connolly et al. 1996; Schwaerzel et al. 2003; Kim et al. 2007). Some of the most prominent dopaminergic projections in the fly brain terminate on the mushroom bodies (Fig. 6) (see Zhang et al. 2007), and mushroom bodies also have a role in modulating sleep (Joiner et al. 2006; Pitman et al. 2006).

INTEGRATING SLEEP SIGNALS IN THE FLY BRAIN

With the demonstration of two separate systems, *Egfr* and dopamine, for regulating sleep, the question arises as to their relationship to each other. Are they sequential? Parallel? Independent? Linked? And what regulates them? The circadian system is a good place to start asking about their regulation, given the major circadian control of this behavior, as well as the effect of certain circadian mutants on it (Shaw et al. 2002; Hendricks et al. 2003b).

Anatomically, both systems are located in the dorsal medial brain and are thus well positioned to receive input from Pdf-containing cells that mediate locomotor rhythms in the brain (Fig. 7) (see Helfrich-Förster et al. 2007). Several of the Pdf-containing cells project to this area, and the suggestion has previously been made that their contacts with cells of the pars intercerebralis may regulate circadian neuropeptide secretion (Kaneko and Hall 2000). Moreover, the pars intercerebralis together with the corpus cardiacum have been suggested to be the developmental equivalent of the mammalian hypothalamic-pituitary axis (Veelaert et al. 1998; Chang et al. 2001; De Velasco et al. 2004; Hartenstein 2006). Because the hypothalamus is a major center in the mammalian brain for the regulation of arousal (Kilduff and Peyron 2000; Saper et al. 2005), and together with the pituitary gland secretes *Egfr* ligands in mammals, it would appear that the pars intercerebralis shares some functional homology with the hypothalamus in its involvement in regulating arousal through neurohormones such as the *Egfr* ligands.

The effects of manipulating dopaminergic transmission and the overt similarity between flies and mammals in the effects of drugs such as methamphetamine (see above) and modafinil (Hendricks et al. 2003a) that affect dopamine transporter activity suggest that there is also considerable

Figure 7. Anatomical location, frontal view, of mushroom bodies, mb (*tan*), dopaminergic system surrounding the mushroom bodies, da (*deep pink*), and pars intercerebralis neurons, pi (*green*) with respect to clock-expressing neurons: LN₄ cells (*orange*); PDF-positive l-LN_v and s-LN_v cells (*red*); PDF-negative s-LN_v cell (*violet*); DN₁, DN₂, and DN₃ cells (*blue*); PER/TIM-expressing LPNs (*olive green*). (Reprinted, with permission, from Helfrich-Förster et al. 2007 [©Wiley-Liss, Inc.].)

functional homology in this system. Dopamine is one of several neuromodulators making up the ascending systems of the mammalian brain (Jones 2005). Shared features of these systems include global effects on brain states, which can be long-lasting, and diffuse anatomical projections. The diffuseness of their projections has led to the suggestion that they function as a sprinkler system in the vertebrate brain, spraying their transmitters over relatively wide areas, rather than in point-to-point synaptic connections. In the fruit fly, these transmitter systems are also diffusely distributed (Monastirioti 1999), although they do not emanate from a centralized brain region and fan out into the brain as in vertebrates.

Whether these systems are closely linked to each other or are independent, as well as the targets of their activity, are open questions. Beyond these circuit considerations, there remains the issue of their relationship to the fundamental function of sleep.

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