Drosophila Behavior Genetics

R. Yamada and E. A. McGraw, University of Queensland, Brisbane, QLD, Australia

Introduction

In the early 1910s, Thomas Hunt Morgan identified the first white-eyed fly in the 'Fly room' at Columbia University. Then, Morgan and his three students, Sturtevant, Bridges, and Muller reported a series of fundamental concepts in the chromosomal theory of heredity, including the sex-linked inheritance of white eyes, recombination and linkage between sex-linked genes, and the first chromosome maps based on linkage. These major scientific breakthroughs were discovered in *Drosophila*, and the field of modern genetics was founded.

Since then, *Drosophila melanogaster* has been one of the major model organisms in genetics. *D. melanogaster* has many benefits for genetic research. It is easy to rear in the laboratory, has a short generation time (10 days at 25 °C), produces large number of progeny (each female can lay over 100 eggs), and has a high tolerance of inbreeding. Moreover, the larval salivary gland contains giant polytene chromosomes that exhibit banding patterns useful in the identification of chromosomal rearrangements and deletions by visual inspection. Thousands of mutations with visible phenotypes served as genetic markers and provided essential tools for genetic analysis. In 1968, Lewis and Bacher described the efficient method of inducing mutation using ethyl methane sulphonate (EMS). EMS mutagenesis facilitates the most important tools of *D. melanogaster*, the power of forward genetic screens to dissect the genes that affect a specific phenotype. In 1980, Nusslein-Volhard and Wieschaus extended this approach to the first large-scale mutagenesis project that attempted to isolate most of genes involved in the embryonic development. Following the discovery of homeobox genes, Lewis, Nusslein-Volhard, and Wieschaus received the Nobel Prize in 1995. With advanced genetic screen techniques such as modifier screens and clonal screens together with genetic transformation techniques, it is possible to screen for almost any biological process, including complex behavior.

William E Castle was the first person to use *Drosophila* for a genetic study in the laboratory at Harvard University in 1901. Subsequently, Castle and his students began to study simple behaviors, including phototaxis (an organisms movement in response to light), geotaxis (response to gravity), and later mechanosensory and olfactory responses. This was followed by a series of studies using more extensive genetic strategies such as quantitative genetic analysis and selection experiments for behavioral phenotypes in *Drosophila* and other organisms including mice and rats. One difficulty in studying the genetics of behavior is that the heritability of behavioral phenotypes is highly sensitive to the environment and genetic background. This is thought to be due to the involvement of multiple gene networks in complex behavior. The consistent conclusion from the early studies was that the genetic basis of behavior is complex and multigenic. Hence, behavior has often been considered a more complex set of phenotypes than either developmental or anatomical defects. Seymour Benzer was the first to report the successful isolation of a behavioral mutant with respect to phototaxis using genetic screens.

Classic Single Gene Mutant Studies of Behavior

The publication of Seymour Benzer's (1967) paper was a seminal moment in the history of behavioral genetics. Before his report, the idea that single genes control complex behavior was not accepted. Traditional approaches to solving the question 'how do genes influence behavior?' had been carried out by selective breeding for the behavioral trait of interest from natural populations. However, Benzer took a different approach, using mutagenesis and genetic manipulations, to quantify a series of behaviors, including phototaxis, circadian rhythms, learning and memory, courtship, etc. His strategy was straightforward: induce mutations by feeding EMS to male flies, screen their offspring for behavioral phenotypes, then use genetic crossing to isolate single-gene mutations responsible for these altered behaviors. Since then, hundreds of scientists have continued Benzer's experimental philosophy and referred to it as 'neurogenetics.'

Circadian Rhythm

Circadian rhythm mutants are one of the excellent examples of the original discoveries in neurogenetics. Circadian rhythms are cycles of behavior and physiology found in nearly all organisms that sets their internal clock time to an approximate 24-h cycle. Circadian rhythm allows organisms to adapt to external environmental factors such as the regular cycles of light and temperature that pervade the biosphere. This clock is conserved in some bacteria, protozoa, plant, and animals, reflecting four billion years of evolution of life on a rotating planet with an oscillating

cycle of day and night. In animals, the rest period in the activity cycle is the best understood aspect of circadian behavior. Most of our current understanding of the molecular basis of circadian rhythm has come from studies in *Drosophila*.

In 1971, Konopka and Benzer performed a simple screen for the phenotype of altered eclosion rhythm and the locomotor rhythms. They identified *period (per)* mutants, the first clock mutants in any organisms. The allele per^0 is arrhythmic; per^s has a short circadian period of 19 h; and per^l exhibits a long circadian period of 29 h instead of the normal 24 h. With the cloning of *per* gene by the groups of Rosbash and Hall, and the group of Young in 1984, *per* transcripts and PER protein were subsequently both shown to oscillate in abundance with circadian rhythms, giving rise to the autoregulatory feedback model of how clock gene products might underlie the core mechanism of the biological clock. Importantly, more recent studies suggest that the molecular basis for the circadian clock is generally conserved between flies and mice. Detailed descriptions of these mechanisms are reviewed by Sehgal and Allada.

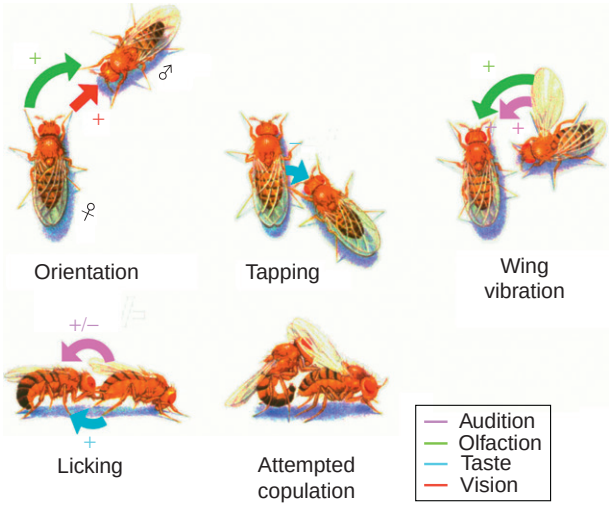

Figure 1 Steps in courtship by *D. melanogaster.* The colored arrows represent the known sensory modalities by which flies communicate: (+) for stimulatory and (–) for inhibitory signals. Reprinted from Greenspan RJ and Ferveur JF (2000) Courtship in *Drosophila*. *Annual Review of Genetics* 34: 205–232, with permission from Annual Review of Genetics.

Courtship Behavior

The earliest descriptive studies of courtship behavior in *Drosophila* were conducted by Sturtevant in the mid 1910s. Bastock and Manning then characterized serial steps of stereotypical actions in males: orientation, tapping, wing vibration, licking, and copulation. This was followed by a series of studies revealing that males and females exchange sensory modalities in each step by visual, acoustic, pheromonal (pheromone: molecule emitted by one individual that alters the behavior or physiology of conspecifics), and tasting signals (**Figure 1**). In 1976, Hotta and Benzer used genetic mosaics (gynandromorphs: flies composed of male and female tissue) to roughly map the portions of the nervous system that control the courtship. Using mosaic analysis, in 1977, Hall refined the techniques and identified anatomical foci in the brain and the thoracic and abdominal nervous system that are required for sex-specific courtship behavior.

The gene *fruitless (fru)* is the best-studied gene involved in courtship behavior. The bisexual *fru* mutant was originally identified as a male-sterile variant in the 1960s. Further studies also revealed that *fru* was required for various aspects of male courtship. The *fru* gene encodes multiple forms of a transcription factor that are required not only for male-specific courtship behavior but also for viability in both sexes. One of the *fru* transcripts is male-specifically spliced and responsible for male-specific courtship behavior. Ectopic expression of the male-specific form of *fru* alters almost every feature of male courtship. A reduction in male-specific *fru* expression in the median bundle exhibits faster copulation, skipping early steps in the behavior such as orientation, tapping, wing vibration, etc. Females ectopically expressing male-specific *fru* show male courtship behavior. Recent studies of specific labeling of neurons that express male-specific *fru* revealed a precise map for core neural circuits involved in male courtship behavior. A set of genes that operate downstream of *fru* remains to be identified.

Male courtship represents an innate behavior, but is also modified by experience. Immature males, in their first day after eclosion, produce female-like pheromones that stimulate mature males to show active courtship toward them with a wing vibration that produces courtship song. Exposure to the song enhances the success in copulation once they are mature. Another example is that male flies tend to exhibit decreased courtship vigor in response to virgin females (receptive) if they have previously experienced rejection from mated females (unreceptive). While these experiments indicate that flies can learn and remember, further analyses are desirable to confirm the experience-dependent modifications in courtship.

Learning and Memory

The first learning mutant, *dunce (dnc)*, was isolated by Quinn, Harris, and Benzer in 1974, using a genetic screen for the Pavlovian olfactory paradigm. In this study, flies were trained to avoid an odor paired with electric shock as a negative reinforcer. After training, the relative avoidance of the shocked odor was scored as a learning index. Using

this paradigm, a series of learning mutant flies were identified, initiating a growing list of genes known to be involved in olfactory memory formation.

The cloning of the *dnc* gene, encoding cAMP phosphodiesterase, and the *rutabaga (rut)* gene, encoding Ca^{2+}/calmodulin-responsive adenylyl cyclase, revealed the importance of cAMP signaling pathways in learning. In addition, both *dnc* and *rut* show preferential expression in a part of the brain called the mushroom bodies (MBs). Considerable evidence supports the importance of MBs as a major structure for olfactory memory and storage. The chemical ablation of MBs disrupted olfactory learning ability and learning mutants show anatomical defects in MBs. The rescue experiment revealed that expression of *rut* activity in the MB neurons of *rut* mutants is sufficient for olfactory memory formation. Using the *Shibire* transgene, a fine genetic tool to block synaptic transmission, it has been revealed that the α/β neuron in MBs are responsible for olfactory memory. While these accumulating evidences support a dominant role for MB neurons in olfactory learning, their relevance to overall memory is still uncertain.

Natural Variation of Behavior in Populations

Most of the mutations identified by genetic screens cause severe perturbation in the function of specific genes well beyond that observed in the natural variation found in wild populations. Genes responsible for a behavioral phenotype are difficult to isolate from natural variants because most behavior is likely to be regulated by multiple gene networks. When this is the case, behavior phenotypes tend to dissipate during the course of crosses for genetic mapping, resulting in a failure to isolate the relevant gene(s). One exception has come from the area of foraging behavior.

Searching for Food: Foraging Behavior

Individual flies in natural populations of *D. melanogaster* can be categorized according to the type of food-searching behavior they exhibit, as either rovers or sitters. Rovers search wider areas for food than sitters. The typical phenotypic frequencies of the two phenotypes in natural populations are 70% rover and 30% sitter. Sokolowski performed density-dependent selection experiments to reveal that rovers are dominant under crowded conditions and sitters under less crowded conditions. The phenotypic differences in behavior are attributed to variation in a single gene called *foraging (for)*. Gene *for* encodes a cGMP-dependent protein kinase (PKG). Rovers have 12% more PKG enzyme activity than sitters, suggesting that this small difference might be sufficient to make variation in behavioral phenotype. These results give us an idea of how behavior is altered and selected in natural populations.

Latitudinal Clines in Clock Genes

The clock gene, period, involved in circadian rhythm (as described earlier), harbors DNA sequence variation in natural populations of *D. melanogaster*. The variation found around the coding region for a threonine-glycine (Thr-Gly) repeat ranges from 14 to 23 copies (**Figure 2(a)**). Recent studies revealed that the distribution of copy number in the Thr-Gly repeat correlates with latitude in both hemispheres. The most frequent alleles in the northern hemisphere are $(Thr\text{-}Gly)_{17}$ and $(Thr\text{-}Gly)_{20}$. The $(Thr\text{-}Gly)_{20}$ variant is more prevalent in the north and the $(Thr\text{-}Gly)_{17}$ in the south. A similar latitudinal cline of the $(Thr\text{-}Gly)_{20}$ variant was also found in Australia, further suggesting the existence of climatic selection (**Figure 2(b)**). Subsequent studies demonstrate that these variants show different circadian temperature compensations and abilities in maintaining a constant circadian period under different environmental temperatures. The $(Thr\text{-}Gly)_{20}$ variants show a very consistent circadian period at different temperatures and exquisite temperature compensation, while the $(Thr\text{-}Gly)_{17}$ variants show poor temperature compensation resulting in shorter circadian periods at lower temperatures. These results suggest that the $(Thr\text{-}Gly)_{20}$ variant might be adapted to the colder and more thermally variable environments at higher latitudes. This thermal explanation for the latitudinal cline of Thr-Gly repeat has been supported by the observation in 'Evolution Canyon' on Mt. Carmel in Israel. The northern-facing slope of this canyon is colder than the southern-facing slope, and the frequencies of $(Thr\text{-}Gly)_{20}$ and $(Thr\text{-}Gly)_{17}$ are significantly different in a manner consistent with a thermal explanation.

A similar natural polymorphism is found in *timeless*, another clock gene involved in circadian rhythms that generates two different length TIM isoforms. The allele generating the longer TIM isoform is more common in the south, while that encoding the shorter isoform is more prevalent in the north in European natural populations of *D. melanogaster*. Although the functional relevance of these polymorphisms remains to be characterized, the studies of natural variation in clock genes provide us with a novel approach for behavioral research leading which can illuminate animal adaptation within an evolutionary and ecological context.

Selection for Aggressive Behavior

Aggression is a complex behavior that is heritable in natural populations of *Drosophila*. Sturtevant reported the first description of fly aggression in 1915. Subsequent

Figure 2 (a) Distribution of *per* alleles in Europe. Frequencies in the various regions for the alleles $(Thr\text{-}Gly)_{20}$ (gray), $(Thr\text{-}Gly)_{17}$ (black), and all other alleles (white). Cited from Costa et al. (1992) and reprinted from Greenspan RJ (2007) The world as we find it. In: *An Introduction to Nervous Systems*, pp. 123–139. New York, NY: Cold Spring Harbor Laboratory Press, with permission from Cold Spring Harbor Laboratory Press. Cited from Costa et al. 1992 and reprinted, with permission of the Cold Spring Harbor Laboratory Press, from Greenspan 2007 Proc Biol Sci. A latitudinal cline in a *Drosophila* clock gene. Costa R, Peixoto AA, Barbujani G, Kyriacou CP. 1992 Oct 22; 250(1327): 43–49. (b) Latitudinal cline of *per* alleles. $(Thr\text{-}Gly)_{20}$ frequency in Australian (blue) and European (red) natural populations. Reprinted from Kyriacou CP, Pexoto AA, Sandrelli F, Costa R, and Tauber E (2008) Clines in clock genes: Fine-tuning circadian rhythms to the environment. *Trends in Genetics* 24: 124–132, with permission from Elsevier.

studies showed the detailed description of the ethological perspective on aggression. In 1988, Hoffmann revealed that enhanced aggression could be achieved by artificial selection experiments. Despite the importance of and ongoing interest in aggression, the gene(s) involved in aggression have never been identified. The complexity of aggressive behavior and the lability of the aggression phenotype make it difficult to perform a standard genetic screen. In 2002, Kravitz and colleagues characterized nine distinct patterns of aggressive behavior, such as fencing, lunging, holding, and boxing, to facilitate a quantitative analysis of aggression. More recent work by Dierick and Greenspan isolated candidate genes involved in aggression, using microarray analysis of selected lines. They developed a population-based selection system to increase aggression in a laboratory strain of *D. melanogaster*, by picking the most aggressive males from a population cage that contained 120 males and 60 females with

multiple territories. After 11 generations of selection, the lines showed more aggression than the control lines. After 21 generations of selection, microarray analysis was performed to characterize genes that were differentially expressed in selected and control lines, instead of taking a traditional genetic mapping approach. Consequently, 42 candidate genes for aggression were found. Subsequent mutant analysis then revealed that a mutation in a gene encoding cytochrome P450 6a20 (*Cyp6a20*) significantly altered aggressive behavior (reviewed by Robin et al., 2007). An independent study by Anderson's group also supports the involvement of *Cyp6a20* in aggression. They showed that social experience increased the expression of *Cyp6a20* to suppress aggression and that *Cyp6a20* is expressed in pheromone-sensing olfactory tissue. These findings revealed that *Cyp6a20* plays a common role mediating heritable and environmental influences on aggression. These studies also represent a more rapid approach for isolating behavioral genes from natural variation.

Courtship Song and Species Recognition

Species Recognition

Species recognition is a major factor in premating reproductive isolation between species. In *Drosophila*, species recognition depends on chemical sensing of pheromones and courtship songs produced by wing vibration. Artificial application of foreign pheromones on the fly body surface is sufficient to induce unusual courtship behavior between different *Drosophila* species. Dummy flies covered with female pheromones can attract males. The male courtship song is not essential for mating, because wingless males are able to copulate although they take longer to be successful. However, making *D. pallidosa* males wingless drastically enhanced interspecies mating with *D. ananassae* females, but reduced intraspecies mating, implying the importance of song for species recognition.

Song Rhythm

The interpulse intervals (IPI), the most important parameter for species recognition, are species-specific and average 35 ms in *D. melanogaster* and 50 ms in *D. simulans*. In 1980, Kyriacou and Hall noted another rhythmic component of song from *D. melanogaster*. The oscillation of IPI, known as the IPI cycle, is also species-specific with a period of around 1 min in *D. melanogaster*, 35–40 s in *D. simulans*, and 75 s in *D. yakuba*. These song rhythms are important for female receptivity, as females prefer their species-specific IPI and IPI cycle for mate choice. Surprisingly, Kyriacou and Hall found that the *period* mutations, which regulate the circadian rhythm described earlier, also altered the song rhythms, with the short-day mutant (per^s) reducing the IPI cycle to ~40 s, the long-day

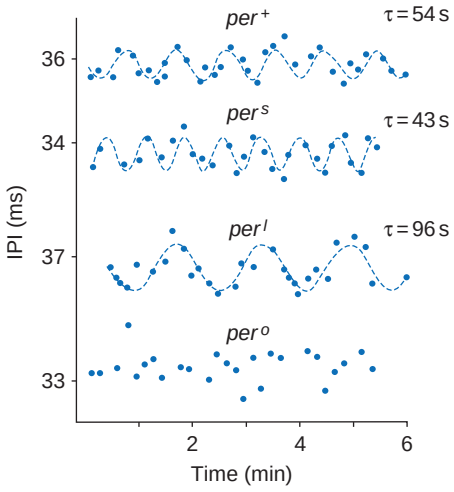

Figure 3 Song rhythms in *per* mutants. Rhythmic oscillation of interpulse interval (IPI) in the male courtship song in normal males (per^+) and per mutant males: short day (per^s), long day (per^l), and arrhythmic (per^0). *t*: the period of the song rhythm. Cited from Kyriacou and Hall 1980 and reprinted, with permission of the Cold Spring Harbor Laboratory Press, from Greenspan 2007 Circadian rhythm mutations in *Drosophila melanogaster* affect short-term fluctuations in the male's courtship song PNAS November 1, 1980 vol. 77 no. 11 6729–6733.

mutant (per^l) extending it to ~80 s, and the per^0 mutatn showing an arrhythmic phenotype in both phenotypes (Figure 3). Interestingly, circadian rhythm and courtship behavior are correlated and likely to be involved in the process of speciation.

Evolution of Song

Kyriacou and Hall mapped the species-specific song rhythms of *D. simulans* and *D. melanogaster* to the X chromosome, a finding coincident with the *per* gene's location on the same chromosome. Subsequent interspecific transformation experiments revealed striking evidence that a *D. melanogaster* male containing a *D. simulans period* transgene sang with the *simulans*-like short cycle, revealing a single gene control of an important species-specific parameter. In contrast, the mean IPI remained intact in the transformants, implying that those two important parameters of song rhythm, IPI and the song cycle, are regulated independently. Similar interspecific transformation experiments revealed that the species-specific mating rhythm is also controlled by *per*.

Different fly species also have distinctive mating rhythms (the pattern of mating with respect to time of day). *D. melanogaster* flies have a peak in their mating rhythm late in the day which is maintained at high levels in the night, while *D. pseudoobscura* flies have two different peaks, one around dusk and the other in the middle of the night (Figure 4(a) left). The *D. melanogaster* transformants carrying a *D. pseudoobscura per* transgene showed a *pseudoobscura*-like peak of mating preference during the

middle of the night in contrast to the *D. melanogaster* pattern (**Figure 4(a)** right bottom). Subsequent studies revealed that if males and females of two types of transformants (carrying the *pseudoobscura per* transgene or the *melanogaster per* transgene) are mixed together, they prefer to mate with flies harboring the same type *per* transgene (**Figure 4(b)**). This assortative mating could be related to the differences of mating rhythm alone, since wingless

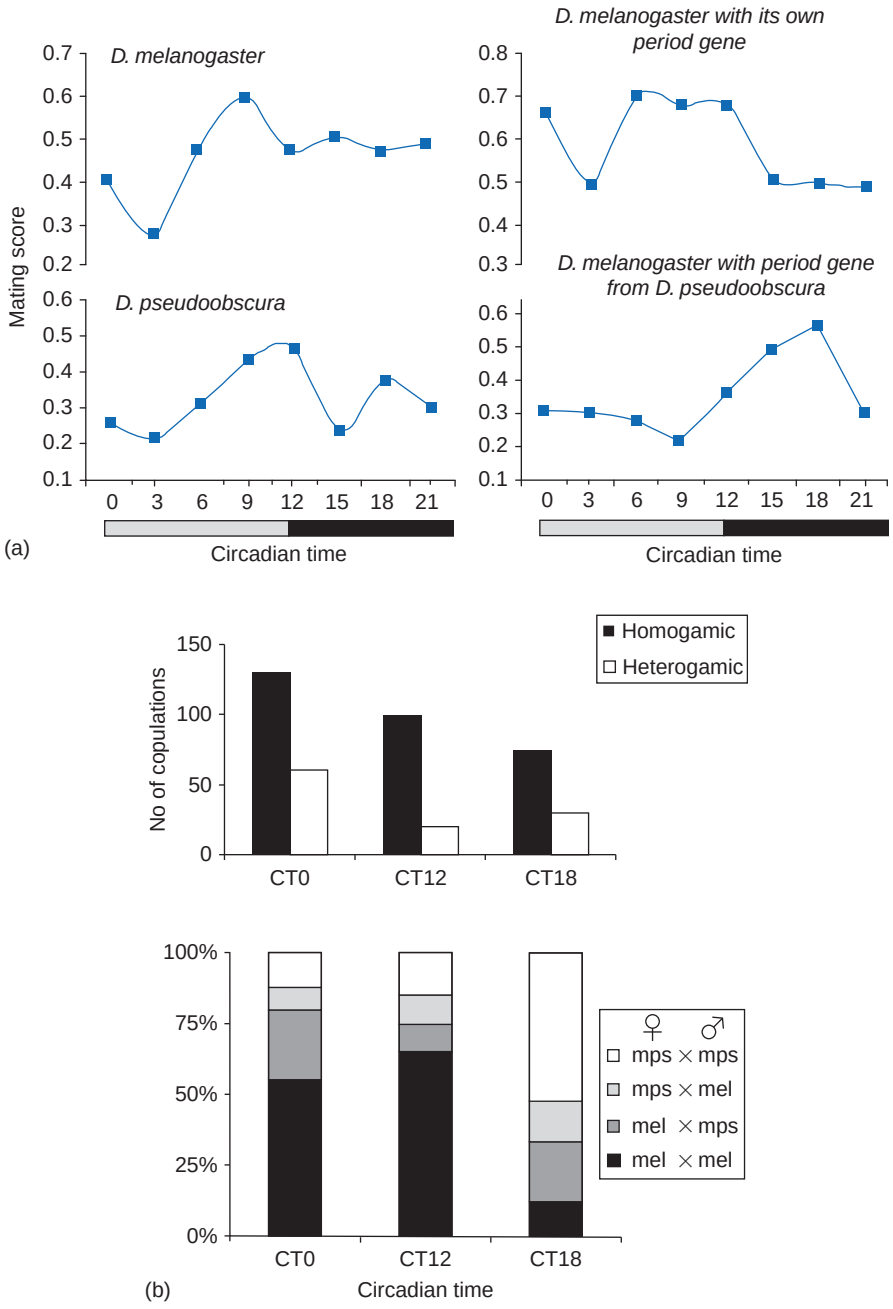

Figure 4 (a) Mating rhythms in *D. melanogaster* and *D. pseudoobscura* (left) and *per* transgenic *Drosophila* (right). Graphs show proportion of pairs mating at various time of day. Genetically engineered transgenic flies carrying the *D. pseudoobscura* period show a peak of mating during the night that is absent in normal *D. melanogaster* but present in normal *D. pseudoobscura*. Cited from Tauber et al. (2003) and reprinted from Greenspan RJ (2007) The world as we find it. In: *An Introduction to Nervous Systems*, pp. 123–139. New York, NY: Cold Spring Harbor Laboratory Press, with permission from Cold Spring Harbor Laboratory Press. (b) Assortative mating in transgenic flies carrying *D. melanogaster per* or *D. pseudoobsucura per*. (top) The number of homogamic mating (black bars, *mel* × *mel* and *mps x mps*) and heterogamic mating (white bars, *mel* × *mps*). *mel*: *D. melanogaster* carrying its own *per* gene, *mps*: *D. melanogaster* carrying *D. pseudoobscura per* gene. (bottom) Relative proportion of the different types of male/female pairings for the data shown in top graph. CT: Circadian time. Reprinted from Tauber E, Roe H, Costa R, Hennessy JM, and Kyriacou CP (2003) Temporal mating isolation driven by a behavioral gene in *Drosophila*. *Current Biology* 13: 140–145, with permission from Elsevier.

males were used in these experiments to avoid any effects of the song rhythm influenced by the *per* transgene (because *per* also alter song rhythm as described earlier).

These studies demonstrated the possible involvement of a single gene, in this case *per*, in the speciation process by influencing both species recognition and mate preference through male song and mating rhythm. However *per* is not likely involved in female song preference as *per* mutant females still prefer the wild-type song rhythm, indicating that the *per* influence on the male song and the female reception are not co-opted. Understanding the genetic basis of female preference is the next challenge for this field.

Bacterial Infection and Insect Behavior

Circadian Rhythm and Immunity

Circadian rhythm is important not only for behavior but also for more basic physiological processes such as immunity. The effects of a disrupted circadian rhythm on infection and disease in mammals are well documented, although the molecular mechanisms underlying these interactions are unknown. Recent studies by Schneider and colleagues have revealed the functional relationship between circadian rhythm and innate immunity in *D. melanogaster*. They found that infection by bacterial pathogens disrupted circadian rhythm, with sick flies moving constantly all day resulting in sleep deprivation. Further studies have shown that circadian mutants per^{01} and tim^{01} died significantly earlier than wild-type control flies when exposed to a lethal dose of pathogenic bacteria. Lee and Edery took a different approach to studying the impact of circadian regulation on immunity. They found that the survival rate of files that are infected with lethal pathogenic bacteria depends on the time of day when they are infected. Flies infected in the middle of the night showed better survival rates (about threefold greater) than flies infected during the day. Similar to Schneider's study, the per^{01} mutant showed higher mortality than the wild-type control in their experiments. These studies provided evidence of a novel interaction between bacteria and fly behavior as well as a new avenue for immunity research, which is applicable to medical strategy based chronobiology.

Influence of *Wolbachia* Symbiont on Behavior

A few studies report symbiont-based behavioral manipulations in *Drosophila*. For example, *Wolbachia* has been shown to increase the male mating rate. *Wolbachia* are maternally inherited intracellular bacteria that infect a broad range of invertebrate hosts. Current estimates suggest that the total number of infected arthropod species might be around 66%, and notably about 30% of flies in the Bloomington *Drosophila* stock center (one of the biggest centers in the world) are infected. *Wolbachia* commonly manipulate host reproduction in a variety of ways, resulting in embryonic lethality, thereby favoring their own persistence and spreading into host populations. While the reproductive phenotype of *Wolbachia* has been studied extensively, little is known about its effects on host behavior, despite its presence in nervous tissues. de Crespigny and colleagues found that *Wolbachia* infected males show higher mating rates than uninfected control males in *D. melanogaster* and *D. simulans*. A recent study by McGraw and colleagues showed that *Wolbachia* infection influences olfactory cued locomotion in *Drosophila* in a species-specific manner. In *D. simulans*, the olfactory response was increased in response to infection, but it decreased in *D. melanogaster*. The influences of *Wolbachia* infection on behavior found in these studies are relatively moderate compared with the differences found in a number of mutant studies. However, because mating rate, locomotion, and olfaction are essential behaviors in nature, the subtle alteration of these behaviors by *Wolbachia* could have a significant impact on their fitness. Further studies are needed to examine the effects of *Wolbachia* in both the laboratory and field. In addition, the genetic and molecular basis of the interaction between *Wolbachia* and host insect remain to be identified. Almost all behavioral genetic studies in *Drosophila* do not mention the *Wolbachia* infection status of the flies studied. Future work in fly behavioral genetics should take into account the presence of the microbe and its possible role in insect behavior.

Conclusion

Neurogenetic research in *Drosophila* paved the way for the fruit fly becoming a model system in the study of complex behaviors such as circadian rhythm, courtship, learning and memory, foraging, aggression, etc. These studies revealed that behavioral genes are pleiotropic. For example, *period* influences circadian rhythm and courtship, *fruitless* is involved in both the development and functioning of the nervous system that regulates various aspects of male courtship, and *foraging* alters food searching, olfactory learning and memory, and epithelial fluid transport. In addition, most of the behavioral mutations turned out to be hypomorphic partial loss of function alleles. One simple explanation is that null mutations tend to be lethal, whereas milder mutations such as those that alter splicing patterns, expression levels, or enzymatic activity, often produce informative behavioral phenotypes. Such 'kinder,' milder mutations are identified through genetic screens of variants from natural population as well as from selection experiments with wild-type strains, instead of through gene disruption strategies such as gene knockout.

These principles from neurogenetics allow us to study complex behavior, using the tiny fly. More recently, van Swinderen demonstrated attention-like processes in *Drosophila* by measuring brain activity responding to visual

stimuli. Shaw and colleagues characterized the behavioral sleep state in *Drosophila* and a subsequent series of studies elucidated striking similarities in features of sleep between human and fly, revealing its regulation by homeostasis and circadian rhythms, the pharmacological responses to drugs such as caffeine, methamphetamine, and antihistamines, and the influence from sex and age. As for sleep, general anesthetics induce immobility and increased arousal thresholds in flies, responses resembling human ones. In addition, with advances in technology, *Drosophila* behavior is now being studied from the diverse lenses of many biological disciplines such as genetics, molecular biology, biochemistry, cell biology, anatomy, and physiology. Consequently, the accumulating evidence and depth of understanding of process and mechanism mean that *Drosophila* has become a medically important model organism, with particular contributions made in the areas of insomnia, drug sensitivity, human neurodegenerative diseases, and even consciousness.

On the other hand, the advent of genome sequencing technology for any organism, together with the ability to test gene function with RNAi in which genetic analysis is not essential, creates the potential for most organisms to become behavioral genetic models. In the near future, it will be possible to study the molecular basis of far more intriguing behaviors than those of the fly, for example social behavior in ants and honeybees, swarming behavior in locusts, and behavioral regulation of host insects by symbionts or parasites. Nevertheless, *Drosophila* has provided us with the state-of-the art technology for behavioral genetic research and will continue to play a pivotal role in this field.

Acknowledgments

The authors thank two anonymous reviewers for their helpful comments on the article. E. A. McGraw and R. Yamada were supported by ARC Discovery Project #DP0557987.

See also: Honeybees; Locusts; *Tribolium*.

Further Reading

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