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The Genetic Basis of Emotional Behavior: Has the Time Come for a *Drosophila* Model?

Konstantin G. Iliadi

Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract: The aim of this review was to summarize the studies potentially relevant to whether *Drosophila* can be used as a genetically tractable model to study the genetic and molecular basis of emotional behavior. Can these studies contribute to a better understanding of neural substrates of abnormal emotional states and specific neuropsychiatric illnesses, such as depression and anxiety?

Keywords: *Drosophila* behavior, anxiety, depression, fear-conditioning, aggression, social interactions

INTRODUCTION

Emotions play an important role in many aspects of adaptive behavior. They are regarded as an essential component in motivating goal-directed behavior (Ressler, 2004), decision-making behavior (Bechara et al., 2000), and cognition (Pessoa, 2008). Charles Darwin carried out the first systematic study of emotions in modern times. In his work titled *The Expression of the Emotions in Man and Animals* (Darwin, 1872), he gave many examples of emotional expressions in man and animals and discussed their significance from an evolutionary point of view. He proposed that all animals need emotions because they tend to increase the chances of survival, and that “even insects express anger, terror, jealousy, and love by their stridulations.” Also, in *The Descent of Man* (chapters 3 and 4), he pointed out that lower animals are excited by the same emotions as humans (Darwin, 1871). However, emotional reactions were not often considered in invertebrate studies, likely due to the difficulty encountered in objectively determining their physiological response. Nevertheless, some scientists believe that emotional awareness is very ancient and widespread in the animal kingdom (Damasio, 2001; Dawkins, 2000; Plutchik, 1984; Rolls, 1999). They argue that all animals need to distinguish between prey and predator, (i.e., become involved in a fight or flight struggle with other organisms). Thus, these animals should display aggression and defense in behavior language or fear and anger in subjective (i.e., emotional) language. Animals need to

explore their environment and orient themselves to find food, shelter, or mates. All these activities are particularly necessary for survival and reproductive functions. According to Plutchik (1984), despite wide variation in the specific behaviors by which these functions are carried out, the basic prototype functions remain invariant throughout the animal kingdom.

First of all, what do we mean by emotions? Unfortunately, this has never been unambiguously formulated. For example, some researchers believe that feeling and emotion are distinct. They used the term “feeling” to refer to the subjective experience or perception. Others believe that emotions can occur unconsciously and thus regard emotion as a more general phenomenon than simple subjective feeling. According to still others, the emotion-provoking stimuli will cause some change in physiological state.

In spite of much disagreement, according to one of the generally accepted theories (Arnold, 1960), any emotional experience proceeds in three steps: 1) perception and appraisal (identification of the external stimulus); 2) emotion (internal state of arousal or feeling arises that may involve physiological effects); and 3) specific behavioral actions (approach, avoidance, attack, or defense, etc.).

One of the key questions that need to be addressed in the studies of animal emotions is the establishment of objective phenotypic markers reflecting emotional expression. Human emotions are expressed throughout the verbal, autonomic (i.e., physiological), and behavioral

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Address correspondence to Konstantin G. Iliadi, Research Institute, Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto Medical Discovery Tower, 101 College Street, East Tower, Toronto, Ontario M5G 1L7, Canada. E-mail: iliadi@sickkids.ca

systems (Oatley and Jenkins, 1998). It is obvious that the first system cannot be used for studies involving nonhuman species, whereas the other two may be relevant, even for invertebrate models.

THE PHYSIOLOGICAL COMPONENT

One of the most obvious signs of emotional arousal is physiological changes in the activity of the autonomic nervous system. There is evidence that at least part of emotional reactions is related to changes in peripheral responses, such as cardiovascular changes (e.g., heart rate and blood pressure), respiratory changes (e.g., breathing frequency), skin temperature and muscle tonicity changes, changes in hormone levels, as well as changes in gastrointestinal motility, which can accompany various emotions. These physiological changes prepare the animal to fully utilize metabolic and other resources in challenging or threatening situations. Whether similar physiological changes occur in invertebrates has not yet been clearly determined. Indeed, there are very few examples showing the effects of stressful disturbances or social interactions on physiological changes. In crayfish, upon anticipation of a social interaction with another crayfish or during an agonistic encounter between animals, both heart and respirator rate show dramatic changes correlating with the intensity of the interaction (Schapker et al., 2002). In contrast to vertebrates, *Drosophila* has an open circulatory system, in which blood (hemolymph) flows freely within the body. Its dorsal vessel is homologous to the vertebrate heart and pumps hemolymph rhythmically (Bodmer & Venkatesh, 1998). It has been shown that neurotransmitters (mainly serotonin) and neural peptides regulate heart rate (Nichols, 2006; Zornik et al., 1999). Interestingly, aging appears to affect heart function and performance in fruit flies in similar ways as it does in humans: an age-related decline in heart function (progressive increase in electrical pacing-induced heart failure as well as in arrhythmias), which probably includes a cardiac autonomous function for the insulin-signaling pathway (Ocorr et al., 2007). Recently, advanced techniques have been developed to measure *in vivo* adult heart rate and the cardiac stress response (Feala et al., 2008; Paternostro et al., 2001; Wessells & Bodmer, 2004). However, these methods are limited to anesthetized flies and, therefore, do not allow for testing the effect of psychogenic (e.g., fear-induced) stress on cardiac response. Given the prospective of developing these methods, it would be interesting to examine the possibility of combining this technique for adult heart-rate measurement with, for example, olfactory conditioning in a restrained fly (Chabaud et al., 2006).

Another intriguing approach to determine a potential physiological consequence of emotional stimulation in

Drosophila is to compare hormone and biogenic amine levels in response to emotional stimuli. Studies in several social insect species suggest that juvenile hormone (JH) may modulate aggression. In honey bees, higher titers of JH were correlated with higher aggression (Pearce et al., 2001). In bumblebees, the dominant social status is achieved through aggressive interactions and associated with high titers of ecdysteroid (Bloch, Hefetz et al., 2000) and JH (Bloch, Borst et al., 2000). There is a growing body of evidence suggesting that the *Drosophila* monoaminergic system is involved in the expression of a number of stress-induced behavioral changes, including aggression (Baier et al., 2002; Hoyer et al., 2008), locomotion (Fox et al., 2006; Saraswati et al., 2004), and associative (i.e., aversive and appetitive) learning (Riemensperger et al., 2005; Schwaerzel et al., 2003; Sitaraman et al., 2008). However, in most of these experiments, the effect of biogenic amines on behavior has been studied by using different genetic manipulations (e.g., mutant and transgenic lines, blocking synaptic transmission, etc.), leaving the question of whether emotional stimuli might induce the marked changes in hemolymph biogenic amines contents unanswered. Future experiments are needed to address these questions.

THE BEHAVIORAL EXPRESSION

Despite different theories addressing the nature and development of emotions, almost all of them assume, at least implicitly, that emotions are expressed through behavior. There are a number of channels through which emotions can become manifest, including actions, facial and bodily expression, voice, etc. Facial expressions of emotion are universal in humans. Some evidence suggests that similar facial expressions can be observed in other primates (Burrows et al., 2006). Postural changes, communicative signals (i.e., vocal and chemical), and locomotor actions in response to emotional stimuli have been described for all vertebrates (Darwin, 1872; Smith, 1977). Are such behavioral expressions observed in insects? Definitely not are the facial expressions. Insects have a chitin exoskeleton that does not allow for the movement of surface muscles that underlie facial expressions. With regard to other behavioral signs, insects, to some extent, can be interpreted as expressing certain types of emotion.

Locomotor Activity and Exploratory Behavior

Locomotor activity is an integrative characteristic of the functional activity of the nervous system. This is an important trait, since it is implicated directly or indirectly in almost all behaviors (Martin, 2003). Locomotor activity in *Drosophila* has been studied extensively and

a variety of measurement techniques have been applied: open-field (Connolly, 1966), maze activity (Ewing, 1963), locomotion measured by locometer (van Dijken et al., 1977), and time-sampling technique (Hay, 1972) that make the four ways of measuring locomotion understandable. Although all these methods have been used to measure locomotor activity, Burnet et al. (1988) pointed out that there are some difficulties in interpreting what the measured activity represents in these studies: amount or speed of locomotor activity, spontaneous activity or reactivity. As emphasized by van Dijken and coauthors (1979), use of various scoring methods may lead only to the firm conclusion that the causation of the behavior depends on the experimental setup. Indeed, different methods can reveal either common behavioral components that are involved in measuring, such as locomotor activity itself, or unique components, including exploratory behavior, latency to enter novel areas, activity suppression in or/and avoidance of anxiogenic zones, and motivation to escape from restraints (Pavlovian freedom reflex; Pavlov & Anrep, 2003).

The role of different *Drosophila* brain structures in the control of locomotor activity has been studied. Using mutant lines that affect the structure of the central complex (CC) in combination with genetic mosaics, Strauss and Heisenberg (1993) have shown that the CC is involved in the control of certain aspects of locomotor behavior, such as walking speed and straightness of walking. These findings were later confirmed by using two independent methods: analysis of the CC mutants and genetic blocking of the CC neurons (Martin et al., 1999). More recently, it has been shown that mushroom bodies (MBs) also play a role in locomotor activity. Chemical ablation of the MB precursor cells, MB mutants, and targeted blocking of the MB all led to an increase in total locomotor activity (Martin et al., 1998).

Changes in locomotor activity in open field tests are positively correlated with emotional reactivity and exploratory behavior in rodents (Denenberg, 1969; Hall, 1934). Those animals that spent more time in the central part of the field are regarded as less fearful and lower in anxiety. Exploration and emotionality are closely and inversely related: high emotionality inhibits exploration, whereas low emotionality facilitates it (Archer, 1973; Lester, 1968).

Interestingly, in the open field, fruit flies show a behavioral pattern quite similar to that of mice and rats. Flies avoid the center of the arena, a phenomenon called centrophobism. Remarkably, this is a sexually dimorphic phenomenon, as females display more obvious avoidance than males. Disruption of the MB function by both hydroxyurea ablation and blocking of neurotransmission has a strong impact on the frequency with which flies enter the central zone of an open field arena (Besson and Martin, 2005); specifically, these flies display a decrease

in avoidance of the central zone. Flies, as well as rodents, also show an initially elevated level of activity when placed in an open field arena (Liu et al., 2007), followed by a decrease in activity to a spontaneous level dependent on both visual and olfactory input. In these studies, Liu and coworkers also observed the effect of centrophobism. As one of the possible explanations for this phenomenon, the researchers hypothesize that flies exhibit strong preference for corners because they are seeking shelter, and this behavior may represent the expression of fear or anxiety in *Drosophila*.

Aggressive Behavior

Aggression is a complex social behavior that contributes to survival and reproduction. According to the classical Moyer's classification system (Moyer, 1968), aggressive behavior may be subdivided into various categories, mainly based on the context in which it occurs: territorial, social conflict, maternal, fear induced, instrumental, etc. Other scientists have proposed alternative classifications that focus on the utility (the usefulness) of the aggressive behavior (Brain, 1979), response patterns of aggression (Flynn, 1976), or functionality of aggression (Wilson, 1975). However, despite these differences, there appears to be little doubt that basic emotions, such as fear and anger, can be related to the majority of aggressive acts. These emotions serve as stimuli for, or causes of, aggressive behavior.

The first detailed description of aggressive behavior in *Drosophila* was published by Jacobs (1960) and revealed that male *Drosophila melanogaster* fight for food sources. Later studies revealed the ecological significance of *Drosophila* aggression in the context of the relationship between mating success and territorial defense (Dow & von Schilcher, 1975; Ringo et al., 1983), as well as heritable and geographic variation in territorial success (Hoffmann, 1987, 1989).

In *Drosophila*, the aggressive behavioral patterns include actions without direct contact with the opponent, such as wing threat, and actions with direct physical contact, including fencing, holding, boxing, and tussling (Chen et al., 2002). Interestingly, wing threat is a threatening posture, often directed to other males before a very quick charge (Dow & von Schilcher, 1975). Does this threatening posture reflect the emotional status (i.e., anger)?

More recently, a number of studies have focused on genetic and neurobiological factors involved in aggressive behavior. These studies can be divided into two categories: 1) studies that focus on the role of biogenic amines in aggression and 2) studies that aim to identify new genes affecting aggressive behavior in *Drosophila*. Mutant flies lacking octopamine show a reduced level of

aggression (Baier et al., 2002). In similar studies using a sophisticated automated video analysis, Hoyer and coworkers (Hoyer et al., 2008) showed that genetic blockage of octopamine biosynthesis results in a strong decrease in male aggression, whereas transgenic rescue of octopamine synthesis in the brain partially rescued this behavioral phenotype. In these studies, to quantify aggression, they used the lunge, one of the key features of *Drosophila* aggression. They also showed that small differences in body size (as small as 8%) play an important role in establishing dominance for the larger male.

The role of serotonin—another biogenic amine—in *Drosophila* aggression is not yet quite clear. Baier et al. (2002) did not observe any significant effect of serotonin treatment on aggression. In addition, between lines selected for low and high levels of aggressive behavior, the expression levels of genes related to serotonin function were indistinguishable (Dierick & Greenspan, 2006). However, the same researchers showed that a drug-induced increase in serotonin level in the fly brain leads to increased aggression (Dierick & Greenspan, 2007). Also, genetically increasing serotonin level in the aminergic cells recapitulated the pharmacological effects, whereas genetic blocking of serotonin release from these cells made the flies behaviorally unresponsive to the drug-induced increase of serotonin, but left them capable of aggression. Both selected lines responded equally to precursor and inhibitor treatment. The researchers thus suggested that selection for aggressiveness did not involve the serotonin circuits or sensitivity to modulation by these circuits. Taking into account the great importance of serotonin for aggressive behavior in a wide range of animal species, further studies will be required.

Dierick and Greenspan (2006) performed a microarray analysis to identify genes that are differentially expressed between the aggressive and neutral lines. They found two genes that produced a direct, significant effect on aggression: cytochrome 450 (CYP450), which is involved in a variety of fundamental physiological functions, including pheromone recognition, and *Obp56a*, an odor-binding protein that also plays a role in pheromone signaling. In similar studies, Edwards et al. (2006) used whole-genome expression analysis and identified 15 novel genes affecting aggressive behavior, eight of which have human orthologs. Another group searched for genes whose expression levels correlate with the influence of social experience on aggression (Wang et al., 2008). Remarkably, among approximately 200 differentially expressed genes, CYP450 exhibited differential expression that was dependent on social experience. It was upregulated by social experience and decreased aggressiveness. In addition, among mutants, aggressiveness was increased in group-housed flies and unaffected in socially isolated flies.

Finally, it has been demonstrated that processes such as learning and memory may contribute to changes in social status. For example, *Drosophila* males appear to learn from previous fighting experiences (Yurkovic et al., 2006). During fights, a socially naïve male may change his behavioral tactic, showing more aggressive acts to become the winner or exhibiting retreating behavior to become the loser. After the establishment of hierarchical relationships, winners progressively attacked more and retreated less, while losers showed the opposite strategy, attacking less and retreating more. Following 30 minutes of separation, these males were re-paired. Losers showed differential fighting strategies against familiar and unfamiliar opponents, but lost to all opponents except other losers.

These results show that *Drosophila* has a wide repertoire of aggressive actions, from the threatening posture to lunging and boxing. In fruit flies, aggressive behavior depends both on genetic factors and environmental influences. Many of the genes essential for *Drosophila* aggressive behavior are conserved and have human homologs (see Edwards et al., 2006). Taken together, these and other studies could lead to more effective ways to search for genes and pathways underlying the pathogenesis of several major human psychiatric disorders associated with aggressive behavior.

Social Behavior

Social behavior may be defined as interactions among individuals, normally within the same species. As part of this phenomenon, the behavior of one individual serves as a stimulus for the behavior of another and vice versa. Generally, social interactions involve a sizeable emotional component, which contribute to the regulation and control of behavior.

In the group situation, flies may influence each other's behavior. Initially, when flies are placed together, they attempt to escape from each other by increasing their run frequency, but quickly terminate runs to avoid collisions and aggressive acts from other flies (Kamyshev et al., 1994). It has been shown that these behavioral changes result from both operant (based on using the trial-and-error method) and classical conditioning. Operant conditioning leads to a gradual reduction of an initially high level of activity, whereas classical conditioning makes it unnecessary for flies to learn the instrumental task again and again, such that in being faced with a similar situation, a fly decreases its activity following presentation of the conditioned stimuli or a specific environment (Kamyshev et al., 2002).

Several studies have demonstrated that social interactions in *Drosophila* may have beneficial effects. For example, it has been shown that social interactions may

be related to cooperative behavior when searching for food (Tinette et al., 2004) and in larval burrowing behavior (Wu et al., 2003), and may influence circadian timing (Levine et al., 2002) and even life-span determination (Ruan & Wu, 2008).

In *Drosophila*, another distinct behavioral element with some function in social behavior is preening. In rodents, preening (also called grooming) is an important part of the rodent behavioral repertoire. Although the primary function of preening is cleaning of the body surface, this behavior has been associated with an arousal process that develops after some stressful events or during habituation to such events, as well as after social or sexual encounters (Spruijt et al., 1992). Thus, preening may serve as a supplementary measure of one or more underlying emotional states (Roth & Katz, 1979).

In *Drosophila*, preening is also regarded as both cleaning and an element of social behavior. Weidmann, for example, “obtained evidence of an increase in preening whenever a male *Drosophila* interrupted his courtship behavior” (cited by Connolly, 1968), and suggested that this behavior may serve as a displacement activity. In a series of elegant experiments, Kevin Connolly (1968) demonstrated that the observed increase in preening in group situations does not reflect the cleaning itself or displacement of sensory hairs following physical contacts between flies. Rather, he suggested that preening serves as a signaling function (largely through the visual modality) facilitating the spacing of animals and thereby reduces the probability of accidental contact.

Definitely, the findings of these early studies suggest that in searching for behavioral markers of emotional states in *Drosophila*, preening warrants more attention. It would be interesting to analyze the preening behavior in the context of aggressive and goal-driven behaviors, as well as in the decision-making process.

Miscellaneous Behaviors

Avoidance Behavior

Animals have several strategies they can use to protect themselves from dangerous situations, including withdrawal (i.e., avoidance or escape) from the danger, immobility (i.e., freezing), defense aggression, and submission (i.e., appeasement) (Marks, 1987). All these behaviors can be induced by fear and thus might have an emotional basis.

However, whether one can consider the escape behavior of *Paramecium* from *Dileptus margaritifer* as fear avoidance is questionable. It is widely accepted that in simple organisms, a response in which the organism moves toward or away from a stimulus is called taxis. In more complex organisms, in addition to these innate

behavioral patterns, avoidance behavior can be advanced through learning.

In *Drosophila*, the innate olfactory avoidance response is mainly associated with olfactory stimulation. Interestingly, depending on the concentration, the same odorants can give both attraction and avoidance signals (Ayyub et al., 1990). Evidence suggests that olfactory information received by the olfactory receptors is transmitted from antennal lobe glomeruli through the antenno-cerebral tracts to the MB and the lateral horn (Heisenberg, 2003). However, until recently, the mechanisms by which a fly discriminates between different odors and the neural circuitry underlying olfactory perception were not quite understood. New findings from Suh and coauthors (2004) show that a distinct behavior response (avoidance) may be triggered by one odorant, which activates one type of receptor and depends on the activity of one glomerulus of the antennal lobe. More important, this specific unknown odorant, which is emitted along with CO₂ by stressed flies (after mechanical or electric shock), is responsible for an innate avoidance behavior that resembles the fear-induced avoidance in higher organisms.

It is also interesting that in our pilot experiments, we found that wild-type flies seem to be differentially responsive to electric shock stimulation, specifically foot-shock presentation. Flies were placed in the chamber with an electric grid and the stimulator was set to deliver a series of 60-V DC shock pulses. The vast majority of flies showed a very obvious behavior pattern. They jumped up in response to the shock pulses and increased their locomotor activity, while a very small number of them became immobilized, that is, resembling the unconditional fear response (freezing) observed in mice and rats.

Many researchers who study *Drosophila*, especially behavioral geneticists, are familiar with the effect of shadow-stimulating activity. When a shadow is quickly passed over the flies, they tend to change their disposition (Angus, 1974). It is, as yet, unclear whether this is a predator avoidance behavior and can be triggered by fear.

Finally, it is critical to understand the similarities between classical and contextual fear conditioning in mammals and *Drosophila* classical olfactory learning and spatial conditioning. As LeDoux (1994) suggested, fear conditioning is an evolutionarily old mechanism for acquiring and storing information about harmful or potentially harmful stimuli and situations. The behavioral expression of conditioned fear and its neural basis appear very similar in all species from fruit fly to human. By definition (summarized by Lewis & Haviland-Jones, 2000), fear conditioning is a type of classical (Pavlovian) learning, in which animals are presented with a neutral (tone, odor) conditioning stimulus (CS) that is paired with an aversive (e.g., foot shock, mechanical shock) unconditioned stimulus (US). The animal learns that the CS predicts the US and will exhibit specific behavioral

responses when the CS is presented alone. In contextual fear conditioning, the context is made up of all of the stimuli present (usually particular environments), rather than the explicit CS (LeDoux, 1996). These conditioning methods have been extensively studied in mammals, both from a molecular and neuroanatomical point of view. In *Drosophila*, learning abilities have also been demonstrated in both classical olfactory and operant conditioning paradigms. In the olfactory avoidance paradigm, the flies can avoid an odor (CS) if it has been associated earlier with electric shocks (US) (Tully & Quinn, 1985). In spatial learning (operant conditioning), which is presumably independent of visual and olfactory cues, flies develop spatial preference in an apparatus called a heat box. There, a single fly, walking freely back and forth in a narrow chamber (box), learns to avoid half of the chamber by being heated immediately upon entering that half. Flies use idiothetic information (i.e., context) for orientation and avoidance of the chamber half that was associated with heat (Putz & Heisenberg, 2002; Wustmann et al., 1996). It is hardly possible to assume that the behavioral response in these paradigms simply reflects a mechanical avoidance; rather, it would be mainly the result of fear conditioning.

Thus, the processes involved in fear conditioning in mammals and avoidance conditioning in *Drosophila* seem to be very similar in their physiological meaning and methodological aspects. Moreover, molecular components of the intracellular signaling cascade underlying fear conditioning in mammals and *Drosophila* olfactory avoidance mainly are similar (see reviews: Davis, 2005; LeDoux, 2003).

Communicative Signals

In animals, communicative signals play an important role in species integrity as well as in predator-induced defense and aggression. These signals may also indicate the presence of danger and promote fear-induced behavior. Studies of insect communication have revealed a wide variety of signals, including acoustical, chemical (e.g., pheromones), and visual.

In insects, an individual emits alarm signals to alert others about potential dangers. Among social insects, such as ants and bees, alarm signals can cause aggregation, dispersion, or defense of the colony (Nunez et al., 1997; Wilson, 1985). In treehoppers, specific vocalizations to alert nymphs of danger have been reported (Cocroft, 1996, 1999). In undisturbed conditions, treehopper nymphs produce few synchronized signals; however, in the presence of a predator (e.g., wasp), they increase their signaling rate by 150-fold. These signals stimulate a response from neighbors and then quickly spread throughout the aggregation, generating a coordinated signal that is longer and greater in amplitude,

compared to an individual's signal. Interestingly, only a coordinated, group signal may induce the mother's defense behavior. Another obvious example of the fear-like cue in insects is the startle signal emitted by male cicadas. During a mating ritual, males sing to attract females. However, in cases of danger (e.g., at the approach of man), one of the males emits an alarm signal and then the other males stop singing (Popov, 1990).

In *Drosophila*, almost all studies of acoustic communications have been restricted to the male's courtship song. There are only a few examples that have focused on other acoustic cues, such as female's "aggressive" or "repelling" songs, which are produced when they are being courted by more than one male at the same time (Donegan & Ewing, 1980; Paillete et al., 1991). In very rare cases, some males courting a fertilized (i.e., unreceptive) female can emit single aggressive signals, which are usually produced during male-male interactions. Interestingly, males from *oc*¹ and *ebo*¹⁰⁴¹ mutant strains with anatomical defects in different parts of the central complex emitted aggressive sounds much more frequently, suggesting an important role for these brain structures in the modulation of acoustic aggressive signals (Popov et al., 2004). It would be interesting to see if male or/and female aggressive actions are accompanied with specific acoustic signals during nonsexual behavior. Do flies emit sounds in response to electric shock or high temperature, etc? Do these sounds have any effect on the behavior of nonshocked flies?

Why *Drosophila*?

Starting from Morgan's first experiments, the fruit fly *D. melanogaster* has served as a workhorse in various fields of the biological sciences. Many studies clearly demonstrate the complexity of *Drosophila* behavior. Flies are capable of both associative and nonassociative learning. For example, hungry flies can learn to run to odors previously associated with a sugar reward, as well as avoid an odor if it has been paired with electric shocks (Tempel et al., 1983; Tully & Quinn, 1985). Flies can also learn to recognize visual, tactile, and spatial cues (Heisenberg et al., 2001; Wustmann & Heisenberg, 1997). Interestingly, male flies also learn to attenuate their courtship behavior after experiencing rejection by a fertilized female (Kamyshev et al., 1999; Siegel & Hall, 1979). Procedures have been developed to study habituation and sensitization (Acevedo et al., 2007; Duerr & Quinn, 1982). Recent studies in *Drosophila* have revealed that flies may exhibit attention-like processes (van Swinderen & Flores, 2007), goal-driven behavioral adaptations (Pick & Strauss, 2005), and decision making (Zhang et al., 2007). *Drosophila* has also become a prominent model organism for studies of antipain drug

research (Manev & Dimitrijevic, 2005), cardiac function (Bier & Bodmer, 2004), aggression (Baier et al., 2002), alcohol intoxication (Wolf et al., 2002), and drug addiction (Wolf, 1999).

With the completion of the *Drosophila* genome-sequencing project, it became evident that many fly and human genes possess significant structural and functional homology (Rubin et al., 2000). This makes it easy to isolate single genes that play a role in behavior by using forward genetic approaches and generate mutations in genes of interest by using a target-selected mutagenesis approach for reverse genetics. The existence of naturally occurring transposable *P*-elements has also been a useful tool to generate mutations via *P*-element insertion or by deletion following imprecise *P*-element excision. The powerful GAL4-UAS ectopic expression system and its modifications, together with a great number of existing transgenic lines, allow for specific spatial and temporal expression of target genes inducing either gain and loss of functional effects or rescue of the mutant phenotype.

One of the major challenges in mammalian animal models is that the behavioral consequences of the expression of a transgene (or any kind of mutation) cannot be assessed, since any observed differences could be entirely accounted for by the use of different genetic backgrounds (Jacobson & Cryan, 2007). Identical mutations give rise to surprisingly divergent phenotypes in different mouse strains (Lipp & Wolfer, 2003). It has been clearly shown that behavior traits are greatly affected by epistatic interactions between the transgene and allele(s) at other loci (i.e., genetic background effect). These traits are highly polygenic and their appearance depends on the intra- and interallelic interactions (Hirsch, 1967). Initially, any transgenic/mutant strain arises from a single individual and, therefore, has only one possible genetic background (i.e., only one set of allelic interactions). Such a strain cannot be compared with any others, because it is impossible to create an identical control strain that will have the same gene combination. The localization of different transgenes can have positive or negative effects on expression. In addition, insertion of the transgene can disrupt the expression of genes at or near the insertion site, which, in its turn, could affect behavior. For the above reasons, all transgenic/mutant strains should be outcrossed for many generations to a wild-type strain to equilibrate the genetic background prior to experiments and have all reasonable genetic controls. While these procedures using mammalian models hardly could be done, they are fairly easy and relatively fast in *Drosophila*. Finally, flies are inexpensive to maintain and have a short generation time (about 2 weeks). *Drosophila* females can produce hundreds of progeny after being inseminated by a single male. Additionally, there are far fewer ethical concerns associated with *in vivo* studies of

Drosophila, compared to those in mammalian model systems.

CONCLUDING REMARKS

The aim of this review was to summarize the studies potentially relevant to whether *Drosophila* can be used as a genetically tractable model to study the genetic and molecular basis of emotional behavior. Can these studies contribute to a better understanding of neural substrates of abnormal emotional state and specific neuropsychiatric illnesses, such as depression and anxiety?

The *Drosophila* multimodal sensory system gathers information about the external world and translates it by means of the nervous system into an appropriate behavioral response. In fact, flies possess a large number of sensory organs that result in the perception of taste, touch, smell, hearing, and vision (see reviews: Ebbs & Amrein, 2007; Gerber & Stocker, 2007; Kernan, 2007; Stocker, 2004; Ting & Lee, 2007). They have a wide repertoire of behaviors discussed previously. Thus, the only question that remains unresolved is whether flies exhibit some physiological changes caused by an emotion-provoking stimulus.

The classification of the emotions is another question still under debate. Many researchers define some emotions as basic or primary, whereas others are complex. According to the Ekman (1984) classification, there are six basic emotions that appear to be innate: happiness, sadness, disgust, fear, anger, and surprise. Panksepp (1982) distinguishes four basic emotional response patterns: panic, rage, expectancy, and fear, which he revealed as consequences of electrical stimulation of areas of the rat brain. Plutchik (1984) has developed a classification model that is a blend of the previous, more basic models. He suggests there are eight basic adaptive reactions (incorporation, rejection, protection, destruction, reproduction, reintegration, orientation, and exploration) that are prototypes, single or in combination, of all emotions. Other researchers have taken different approaches to classify emotions, which often overlap or/and deviate from those classifications that already exist. It is definitely hard to believe, or more precisely identify, that emotions such as jealousy and love (by Darwin's interpretation) may be present in flies. However, emotions such as fear and anger, which underlie anxiety and depression, may, indeed, be there. Interesting, the potential for fruit flies to be used to study anxiety and depression has been stated several times (Belzung & Philpott, 2007; Damasio, 2001; Kalueff et al., 2007; Moldin, 2000). To date, *Drosophila* has been successfully used as a model system to elucidate molecular, physiological, and behavioral mechanisms of several human neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's (Chan & Bonini, 2000).

Remarkably, *Drosophila* shares with rodents and humans essential neurochemical substrates (e.g., specific receptors, enzymes signaling proteins, and neurotransmitter systems), which are involved in the control and regulation of emotional behavior (Finn et al., 2003; Tarantino & Bucan, 2000). All these findings suggest that our understanding of the genetic and cellular mechanisms underlying emotional behavior can be vastly improved by using the fruit fly as a genetically tractable model system.

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