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Innate preference in *Drosophila melanogaster*

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Innate preference behaviors are fundamental for animal survival. They actually form the basis for many animal complex behaviors. Recent years have seen significant progresses in disclosing the molecular and neural mechanism underlying animal innate preferences, especially in *Drosophila*. In this review, I will review these studies according to the sensory modalities adopted for preference assaying, such as vision, olfaction, thermal sensation. The behavioral strategies and the theoretic models for the formation of innate preferences are also reviewed and discussed.

***Drosophila*, innate preference, tactic behavior, sensation**

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Compared with learned behavior, an innate behavior is what an animal can do without practice or training. Animal innate preference behavior is largely the primitive reaction that an animal spontaneously demonstrates when choosing between different environmental conditions, such as light, odorant, temperature, or different objects like visual targets and food.

Innate preference behaviors are the cornerstones of more complex behaviors. For example, in associative learning behavioral paradigms, the unconditional stimulations, no matter aversive or rewarding, are designed based on innate preferences. In the classical Palvnovian conditioning, food award to the dog is used as unconditioned stimulus. In *Drosophila* classical olfactory conditioning, avoidance to electrical shock as well as the two odors as conditioning cues is required [1]. In *Drosophila* visual operant conditioning in a flight simulator, escaping the heatshock punishment is crucial for successful training [2,3]. As such behavior paradigms themselves are relatively complicated, it is necessary to understand how the fundamental behavior is organized at neural and molecular level, before a full understanding of the complex behavior can be achieved.

As animals generally demonstrate biased preference when facing sensory stimulation in the same modality but of different properties, preference behavioral assays are widely used to study sensory abilities of the animals. In such cases, cautions must be taken when drawing a conclusion because defective preference does not necessarily result from abnormal sensation ability although defective sensory ability must lead to abnormal preference.

1 Behavioral organization of preference

The commonly mentioned "preference" generally refers to biased choice between two or more conditions in the same sensory modality but of different quantity or quality, for example, preference between different light conditions, such as different light intensity, different light color, or different olfactory conditions such as certain odor at different concentrations, or different temperatures. The simplest form of preference is the choice between two conditions, which is widely adopted in many experimental studies. In more complicated preference situations, choice can be made between more alternative conditions, including various combinations of different conditions.

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In experimental studies, various forms of paradigms are used to evaluate innate preference behavior. In *Drosophila*, preferences in different sensory modalities, visual, olfactory, chemical, as well as thermal preference, are well studied. At behavioral level, innate preference can be measured by difference types of motion output. Though behavioral responses such as *Drosophila* proboscis extension, larval body rolling and head swing [4–8] are adopted by some researchers to study preference behavior, tactic behaviors are most widely used for preference evaluation, like phototaxis, odortaxis, thermotaxis, chemotaxis and so on. The reason probably lies in that the translocation of animal position is easier to be monitored and tracked. Most of the studies that I am going to introduce are based on tactic behavior.

2 Innate *Drosophila* preference studies in various sensory modalities

In recent years, study of innate preference behavior has made the most distinguished progress in *Drosophila*. The preferences we mention here are mainly choice between two different conditions.

2.1 Visual preferences

Drosophila melanogaster has long been known to be phototactically positive in adult and negative in larval stages. However, the molecular and neural basis of phototaxis is still largely unknown.

2.1.1 Visual preference in adult flies

The adult fly phototaxis assays were performed in a T-maze or a serial network of Y-maze [9–12]. Currently, most adult fly phototaxis analysis used for color preference (or spectral wavelength preference) are generally performed in a T-maze, in which the flies are first placed in between two tubes that are respectively lighted in different colors, generally UV/green, UV/blue or green/blue [13,14–16].

For quite a long time, the study of mechanism underlying adult fly phototaxis was performed on the level of retina. Among the eight different types of ommatidia cells, R1-6 are responsible for motion detection as well as dim light detection, thus are largely irresponsible for regular phototaxis behavior. Rather, the color-sensitive R7 and R8 play more important roles in mediating regular phototaxis [17,18].

The retina-decided visual spectral preference was recently elaborated by Yamaguchi *et al*. [15]. In a "UV vs. blue" choice, flies with only R1-R6, as well as flies with only R7/R8 photoreceptors, preferred blue, suggesting a non-additive interaction between the two major subsystems. Flies defective for UV-sensitive R7 function preferred blue, whereas flies defective for either type of R8 (blue- or green-sensitive) preferred UV. In a "blue vs. green" choice, flies defective for R8 (blue) preferred green, whereas those defective for R8 (green) preferred blue.

Mechanism studies of spectral preference deep into the optic lobe were first led by Lee lab from National Institute of Health, USA. In 2008, they reported that DM8 amacrine neurons spanning different layers of fly optic lobes receive input from 13–16 UV-sensing R7s and provide output to projection neurons. These DM8 neurons are both necessary and sufficient for flies to exhibit phototaxis toward ultraviolet in a UV/green light preference assay [14]. Combining with the result of Yamaguchi *et al*., these results suggest that R7-DM8 pathway favors fly's preference for UV light.

2.1.2 Larval visual preference

Larva flies are well known to avoid light. Light avoidance in larva has been established to rely on larval eyes—the Bolwig's organs, which later develop into adult eyelet. Killing or inhibiting the Rh5-expressing photoreceptors but not the Rh6 photoreceptors of the Bolwig's organ leads to blindness in larva and consequently lack of larval phototaxis [19,20]. Downstream to the photoreceptor neurons, the larval circadian neurons play important roles in regulating larval phototaxis. The timeless-expressing TIM neurons that do not express Cry (cryptochrome) and PDF (pigment dispersing factor), i.e., the 5th LN (lateral neuron) and DN2 (dorsal neuron) are necessary for larval light avoidance [19,20]. The neurotransmitter ChAT working between BN and TIM neurons carries the visual information that is required for rapid light avoidance response. Even downstream to the circadian neurons, the larval central brain NP394 neurons that directly receive input from the PDF-expressing circadian neurons pivot larval preference between light and darkness—activation of NP394 neuron prompts larva to the darkness whereas inhibiting NP394 neurons drives larva toward light [21]. These results together make a complicated neural network that process larval visual information required for phototaxis behavior.

It is worth noting that using a head swing-based preference assay, Xiang *et al.* [8] found that the multi-dendritic neurons distributed around the whole body surface could serve as photoreceptors to mediate larva's aversive head swing response to strong UV light.

Taken together, the most profound progress is mainly in disclosing the neural basis of fly visual preference behavior. The underlying neural circuits have been extended from the photoreceptor level to higher class downstream neurons in visual processing pathway.

2.2 Olfactory preference

The measurement of olfactory preference generally adopts the so-called odortaxis paradigms in which the flies choose to go toward or to leave a place associated with a certain odor. There are various forms of odortaxis. Like in visual

preference (phototaxis), a simple T-maze can be used to evaluate the preference between two types of odors [22]. Or, a so-called olfactometer can be used to measure the adult fly's tactic response towards a single odorant [23,24]. In the case of larva odortaxis, the odor sources are positioned in serials in defined holes in either plastic plate cells or in agar plate. The larvae can sense the diffused odor gradient and demonstrate attraction or aversion along the odor diffusion gradient [25,26]. Here I have to point out that I use the word "odortaxis" for fly's tactic response to odorants and "chemotaxis" for those responses to non-voltatile chemicals in liquid or solid form.

2.2.1 Adult olfactory preference

As numerous olfactory sensory receptors to various odors have been identified, the behavioral measurement of olfactory preference is elaborated for most odors [27,28]. One must-say case of olfactory preference study is the work done in an easy-to-ignore odor, CO_2, which cannot be sensed by human beings but can be sensed by fruitflies. Flies generally tend to avoid CO_2, which can work as a stress odor that a fly release when it feels stressed. Suh *et al*. [24] showed that CO_2 can induce an innate olfactory avoidance of a Drosophila as stress odor by stimulating a complex receptor that is composed of two different G protein coupled receptors Gr21a and Gr63a. CO_2 is sensed by a single glomerulus in the antennal lobe, the V glomerulus which is not activated by any other odorants that have been tested [24]. More interestingly, exciting only the CO_2 sensory neurons using an optogenetic tool of ChR2 could sufficiently induce avoidance-like behavior, further confirming that CO_2 sensory neurons can induce avoidance response [29].

In adult flies, olfactory preference was shown to be determined at olfactory glomerulus. Wang lab reported in 2009 that the DM1 and VA2 glomeruli are both sufficient and necessary for odor attraction, whereas DM5 glomerulus mediates aversion response to odors [24]. It is proposed that two pathways, which channel attraction and aversion respectively interact to decide if the fly will be attracted by an odor or repelled by an odor. This is an important discovery in the study of preference behavior since it showed at least the following points: (i) preference can be decided at the level of synaptic connection between first class sensory neurons and secondary internal neurons; (ii) preference can be explained by a competing pathway model.

2.2.2 Larval olfactory preference

Larval fly's preference response to different odors has been systematically investigated by Leslie lab and Carlson lab [25,30]. Despite the morphological and developmental differences, the larval olfactory system, including odorant receptors, as well as the neural circuit organization, is pretty much like that of the adult, except that the former is simpler [31].

The olfactory sensory neurons (OSN) in larva for odortaxis is highly redundant and coordination between different OSNs is quite popular [32]. Actually, one sensory neuron at one side of the body is sufficient to stimulate odortaxis behavior. Nevertheless, two side neurons can coordinate to improve the odorant detection and performance of odortaxis [26].

Since the olfactory receptors and neurons corresponding to a large number of odorant molecules have been well studied, the molecular and neural basis at the sensory neuron level for fly olfactory preference is quite clear. As the underlying neural circuit extends to the secondary neurons at the glomerulus level, it is hopeful that the neural circuit underlying olfactory preference can be largely resolved in foreseeable future.

2.3 Thermal preference

Drosophila is an ectotherm whose body temperature changes according to environmental temperature. Most thermal preference studies carried out in *Drosophila* adopt thermotaxis assay, in which a group of larval or adult flies demonstrate thermotaxis along a thermal gradient [33]. Flies will choose their favorite temperature by either negative (towards the coolness) or positive thermotaxis (towards the warmth) [34,35].

2.3.1 Adult thermotaxis

In adult fly thermal preference, it is interesting that TRPA1 is required for warmth avoidance. TRPA1 functions in a small set of so called warmth-activated anterior cells (AC) located in adult brain. Flies with dysfunctional AC or mutant TRPA1 demonstrated reduced or eliminated warmth-avoidance behavior [36].

Kim group from Korea screened a huge batch of flies and concluded that the mushroom body plays an important role in thermotaxis and the cAMP signaling pathway in mushroom body neurons is the molecular key that decides the favorite temperature of a fly [37].

Most recently, researchers from Zuker lab identified TRP family gene expressed in antenna, *brivido*, to be necessary for avoidance response to cold temperature and thus positive thermotaxis. More interestingly, they found *brivido* was expressed in three of six neurons in arista, and the rest three neurons are responsive to warm sensation and negative phototaxis. The HOT and COLD neurons project onto distinct but adjacent glomeruli in the proximal-antennal-protocerebrum (PAP) to form a thermotopic map in central brain [38].

2.3.2 Larval thermotaxis

In larval flies, various types of thermosensors have been identified. At body surface of larva, terminal Johnston's organs are responsible for coolness sensation (11 or 18°C) and consequently the larval avoidance to coolness [39], while Pyrexia and Painless expressing multidendritic neu-

rons are required for larval sensation of high temperature of more than 35°C and nociceptive 42°C [7,40]. In addition to the traditional surface thermal sensory organs, there are internal thermal sensory neurons. Scientists from Garrity lab found that larval TRPA1 and TRPA1-expressing neurons were responsive to excessive warm temperature (25°C and higher) and consequently required for avoidance to warmth. On the other hand, TRP and TRPL are required for larval avoidance to excessive cool temperature [41,42]. Furthermore, scientists from Montell lab investigated the more subtle thermal preference between 18 and 24°C, and found that a series of TRP family members are required. The TRPV family member, IAV in chordotonal organs is required for positive thermotaxis in 17.5°C over 14–16°C choice, while the TRPA family members NORPA and TRPA1 are required for negative thermotaxis in 18°C over 19–24°C choice [43,44]. It is noteworthy that TRPA1 works downstream to the PLC signaling pathway, but not as a direct thermosensor, in mediating the subtle thermal preference (negative phototaxis). Together, the neurons that have been discovered to be involved in larval thermotaxis are mostly peripheral neurons such as IAV-expressing chordotonal organs, NORPA-expressing multidendritic neurons, as well as TRPA1-expressing neurons in the mouth-peripheral regions. TRP family member proteins make up the large part of the known molecular basis of thermotaxis, except that the PLC signaling pathway is implicated in subtle thermal preference in the 18°C over 19–24°C assay.

Matuno lab from Japan studied thermotaxis from another aspect. They reported that larval flies with defect in a mitochondria protein, the *Drosophila* ortholog of dystroglycan (DmDG), showed higher tolerance to cold as well as preference for low temperature. These flies showed higher metabolic rate and faster energy generation for maintenance of body temperature, so that they preferred to stay in environment of relatively lower temperature. On the other hand, overexpression of this protein resulted in reduced energy generation and consequently fly preference for relatively higher temperature [45].

A more striking but interesting discovery is that the photosensitive rhodopsin-coding gene ninaE expressed in larval body wall cells that expresses trpA1 is also required for larval thermotaxis that involves discrimination between 18 and 24°C [46]. Replacing ninaE with other functional opsins (except Rh3) does not affect larval thermal discrimination ability.

So far, a lot of data concerning the molecular and neural basis of fly thermal preference has accumulated, but the identified neurons are largely at the sensory neuron level. Although central brain structures such as mushroom bodies have been implicated in this process, their connection with sensory neurons is missing. One future task is that the functional neurons can be eventually interconnected to form a neural circuit accounting for thermal preference.

2.4 Chemical preference (chemotaxis)

Chemical preference behaviors are generally assayed in various ways, such as chemotaxis or proboscis extension in gustatory test [47].

A two-way choice assay is generally used for chemotaxis to study the fly preference for different non-voltatile chemicals [48]. The starved flies are placed into 72 well microtiter dishes containing one of two types of test chemicals in alternating cells. Each chemical is mixed with a dye of a certain color while the other with dye of a different color. The flies with different colors in abdomen were determined to evaluate the preference [49].

As a large number of chemicals are sensed by tasting, gustatory dependent chemotaxis relies heavily on the normal function of the gustatory system [50]. So far, in addition to GR66a and GR93a which are required to prevent ingestion of caffeine [51,52], gustatory receptor GR33a, which is widely expressed in GRNs that respond to aversive chemicals, is required for avoiding nonvolatile repellent chemicals [49]. In all these cases, chemotaxis was adopted to analyze the chemical preference. Gr5a, together with Gr64a and Gr64f, are shown to work together to enable sugar detection and mediating the preference between different sorts of sugars or sugar solutions of different concentrations [53,54]. Among the gustatory receptors, Gr33a and Gr66a are expressed in labella/labellum, Gr93a is expressed in labellum and pharynx, and Gr5a is expressed in labellum and distal segments in the leg. All of them are expressed in body surface sensory neurons, but not the internal neurons [49].

In *Drosophila* chemotaxis, TRPA1, again, was reported to be involved. TRPA1 was found to be expressed in GRNs (gustatory receptor neurons) that respond to aversive compounds such as bitter compounds like caffeine, quinine and strychnine. TRPA1, required in a subset of avoidance GRNs, was behaviorally responsive exclusively to aristolochic acid. What is more, TRPA1 activation by PLC signaling is required for avoiding aristolochic acid [55].

One prominent chemical preference demonstrated by the fly is the preference for water. The proboscis extension assay was used to study water sensation. In this assay, the thirsty adult fly will extend its proboscis when presented with water. In the year of 2010, the groups of K Scott and Z Wang independently reported that ppk28, a amiloride-sensitive epithelial Na^+ channel, is essential for *Drosophila* gustatory water reception [4,5].

Interestingly, based on a food substance preference assay (the number of flies on each food substance), the CO_2 dissolved in water, or carbonated water, is sensed by the E409 neurons in the proboscis labellum, different from the volatile CO_2 that is sensed by the olfactory sensor Gr21a and Gr63a and the corresponding neurons at antenna [56]. Thus the olfactory CO_2 and gustatory CO_2 signals are processed completely independently.

2.5 Geotaxis

Negative geotaxis is a simple taxis behavior that an adult fly demonstrates to climb up the wall of the container. The Johnston's organ that can sense mechanical pressure plays an important role in mediating geotaxis. Mutants in TRPA family genes such as painless, pyrexia, Nanchuang and IAV are defective in negative geotaxis [57]. However, the Johnstons organ that is positioned at body surface is not the only geotaxis-deciding center. The PDF and its receptors in the central brain have been shown to be required for normal negative geotaxis [58,59]. Also, disruption of central complex in adult fly brain could abolish negative geotaxis in adult flies [60].

3 The navigational strategy of taxis-based preference behavior

Preference is the ultimate behavioral outcome, how it is finally achieved? It is necessary to study the details of the movement processes involved in the choice behavior, since this can provide us with more direct understanding of the innate preference behavior.

The navigational strategy that the animal adopts to fulfill the preference behavior was intensively analyzed in larval taxis-based preference behaviors [26,61,62]. In presence of an odorant gradient, Louis *et al*. [26] showed that normal larvae were able to orient their motion directly toward the direction of the largest concentration increase, by locally computing the heading angle between the direction of the odorant gradient and the direction of instantaneous motion at every point of a path. Such alignment increases as the odorant concentration increases. In mutant larvae of $Or83b^{-/-}$ which was defective in olfaction, the alignment was not obvious.

The taxis strategy was systematically investigated in larval thermotaxis along a thermal gradient. Luo *et al*. [61] studied first instar larval navigational movement on a continuous thermal gradient with a tracking microscope. They divided larval movement into two types: runs and turnings. Running can be understood as going to a favorable place whereas turning suggests that the place ahead is unfavorable. The duration, direction and speed of each running period (in between turnings), as well as the rate of turning, the size of turning angle, were statistically analyzed. It is the properties of runs and turning (such as duration, direction and speed for run; rate of turning and size of turning angle, and so on) that jointly decide the larval trajectory and correspondingly the final preference outcome.

In both reports, *Drosophila* larva showed specific orientation change upon gradient-like conditional change. This is different from that of the biased random walks of motile bacteria and *C. elegans* which changes the direction between runs randomly and do not depend on the direction of the stimulus gradient [61,63–65]. Therefore, this raises a question: how the gradient can induce re-orientation in larval fly? One possibility is that the sensory organs are spatially distributed so that the different condition can be sensed at one time by sensors across body parts. It is the spatially different sensation that generates a re-orientation response. Another possibility is that the fly compares what it senses now and what it sensed a moment ago. It is the temporally different sensation that drives the larva to move forward or to make a turn. The second is more likely when sensory input is limited to a restricted body region, as evidenced by Luo *et al*. [61]. In such cases, working memory or short-term memory is needed to make such temporal comparison possible. Thus, it is expected that a mutant defective in working memory will show loss of preference. The memory component should be taken into consideration in the behavioral strategy study, for an ultimate understanding of preference behavior.

The analysis of preference behavior must also be paradigm-specific. The way the paradigm is designed significantly affects the animal's navigational strategy and preference outcome. In the continuous or continual gradient environment, the animal keeps facing condition change all the time. It is the gradient that decides the movement of the animal. In other paradigms of preference, the thing can be different. For example, in a simple dark/light preference test [20,56], the arena contains simply a dark half and a light half, so that there is only one dark/light change. Other than the time for passing the light/dark boundary, the larvae spend their time staying in dark or light areas with no change in light intensity. In this case, the final spatial distribution, or the preference, of larvae is decided not only by the response of larvae to light/dark switch, but also by the movement difference in between dark and light conditions. The latter can even contribute more to the final preference outcome [62]. Such analysis was in consistent with the report by Louis *et al*. in 2008, in which larval turning rate, suggestive of dislike, was reduced at higher odorant (isoamyl acetate) concentrations [26]. The impact of each factor on animal preference depends on how much they function in the paradigms to affect the final outcome.

Based on the above mentioned reports, it is obvious that at least for taxis-based larval preference, similar movement patterns are involved. This means that common components are required for preference behaviors in various sensory modalities. To go further, it is interesting to postulate that there exists a common preference center for various forms of preference behaviors. At least, we can hypothesize that the motor neurons and probably immediate upstream motion control neurons are commonly involved in different preference behaviors. It will be fascinating to find out the convergence site of different sensory-motor pathways and to discover how the corresponding neurons function to enable the preference behavior. If such a "preference center" can be found, it will open a door to the full understanding of

integration of sensory information.

4 Theoretical models for preference

There are at least two possible theoretic explanations for preference outcome. Take the two-alternative choice preference for example, it is easy for us to assume that there is one neural signal processing pathway responsible for choosing one of the alternative, and there is another pathway hosting the choice for the other alternative. The outcome of preference behavior depends on the competition result of these two pathways: If the pathway for alternative A overwhelms, the animal prefers A; or else, it prefers B. This model is supported by several studies [15,24]. However, so far there is no evidence at the wholesome neural circuit level to show that there exist such antagonizing pathways.

Another way of explanation is that one single neural signal processing pathway regulates the preference outcome depending on the activity status of the pathway. The activity level in a certain range enables an approaching behavioral response, whereas the activity level in other ranges leads to aversive behavior. Our data that inhibiting the activity of larval NP394 neurons could induce the originally photophobic larvae to prefer the light over darkness, can be explained in this way [21,66].

Nevertheless, the above mentioned theoretic models are not mutually exclusive since we can consider the two pathways in the first model as one whole larger network as in the second model.

5 Conclusion

By reviewing and discussing the most recent progress in studies of *Drosophila* innate preference behaviors, we conclude that the molecular and neural basis for these preference behaviors is quite diverse. No common molecules or neurons are found to be involved in different types of preference behaviors, except that TRPA1 is shared by larval thermotaxis and larval chemotaxis, and that larval multi-dendritic neurons are occasionally shared by larval thermotaxis and phototaxis. However, we cannot conclude that there is no common in mechanisms underlying different types of preferences, since most of the accumulated data are limited to the level of primary sensation. Actually, there are signs that similarities between larval navigational strategy in thermotaxis and odortaxis can be found. It will be fascinating to look for the common basis across different preference behaviors of various modalities, but probably only after the full molecular and neural underlying mechanism is disclosed.

I address my apology to authors whose work is importantly related to but not cited in this review, since rapid progress is being made in this research field. I thank Dr. Liu Li for critic comments on the manuscript. This work was supported by the National Natural Science Foundation of China (Grant No. 31070944).

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