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Drosophila melanogaster: A Platform to Study Therapeutic Neuromodulating Interventions

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ABSTRACT: The *Drosophila melanogaster* (fruit fly), is a crucial and straightforward model organism for researching how genetic changes affect behavior and neural activity. Drosophila is used by biologists to study the nervous system because of its genetic tractability, well-known complex behaviors, straightforward neuroanatomy, and numerous human genes orthologs. Due to the Drosophila central nervous system's diminutive size, neurochemical studies are difficult. Recently, electrochemistry-based techniques have been created to monitor the release and clearance of neurotransmitters in real time in both larvae and adults. So, in this study Drosophila models used to study neuromodulator activity were reviewed and compiled using various databases. It is possible to take a close look at the functional role of traditional neuromodulators like octopamine, serotonin, dopamine, and neuropeptides using the genetic toolkit of Drosophila. This study compiles neurotransmitter role such as dopamine, serotonin, and octopamine production in both genetically normal and mutant flies. The fly is a system that is well-suited to shed new light on the complex issue of how neuromodulation might link behavioral demands particular to a given scenario with the level of arousal in the brain. The fly has powerful genetic tools and increasingly well-defined behavioral circuits.

INTRODUCTION

The brain is in charge of regulating metabolism, behavior, and food intake in order to maintain energy homeostasis. It does this by monitoring nutritional status and making appropriate modifications to these factors [1,2]. Neuromodulators, and other metabolic and feeding-related brain systems are evolutionarily conserved between mammals and invertebrates. The cost of conducting trials and the enormous complexity of the brain make it difficult to study neuromodulators in mammals [3]. A significant invertebrate genetic model system, Drosophila (the fly), is used to solve these challenges [4].

There has been evidence that serotonin (5-HT) regulates appetite, somatogastric responses, and food intake [5]. Octoctopamine also modulates feeding and is regulated by fly homologs of obesity-linked genes [6]. A number of studies have shown that neuropeptide F regulates feeding in response to feeding-associated signals [7]; and normal food intake requires dopamine signaling [8].

Neuromodulators have a significant impact on animal behavior by influencing the activity of clusters of neurons. The complicated male courting desire is under neuromodulatory regulation. Tyramine (biogenic amine) related to dopamine, functions are unknown in most of the animals has shown to affect neurons of inferior posterior slope (IPS) in the Drosophila melanogaster brain. Male courting behavior was dramatically increased once TyrR (a tyramine-specific receptor) that was expressed in IPS neurons was lost. Mutant males of TyrRGal4 showed a wild-type preference for females, hence this impact only materialized in the absence of females. Male-male courting significantly increased when IPS neurons were artificially activated to the contrary of what happened when IPS activity was suppressed. The results of the study indicate that TyrR functions as an inhibitory neuromodulator to lower the level of courting activity [9].

For the purpose of identifying neural substrates of behavior, actions must be defined in terms that relate to brain activity. Motor neurons produce signals that correlate brain and muscle activity, but it has been difficult to define behavior in terms of muscle contractions apart from simple movements. Using

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comprehensive single-cell imaging to map the muscle activation of the pupal fruit fly, researches describe a multiphasic behavioral sequence in Drosophila. A convolutional neural network allows us to extract major movements by identifying a previously undescribed behavioral phase. According to this study, muscle activity varies a great deal, and stereotypy increases sequentially in response to neuromodulation. A platform like this can be used for studying whole-animal behavior at a cellular level, quantifying its variability across multiple spatiotemporal scales, and quantifying its neuromodulatory regulation.[10].

The genetic toolset of Drosophila offers the opportunity to study the function of classical neuromodulators like dopamine, 5-HT, octopamine, and neuropeptides in detail. Various mechanisms have been identified in recent years that modify chemosensory perception and processing in response to internal states, such as hunger and reproductive status, but future research should investigate the mechanisms underlying other internal states, such as the modulatory influence of endogenous microbiota. Additionally, illness brought on by a pathogenic infection may provide new insights into the neuromodulators circuits integrating detrimental post-taste signal in the circuits controlling olfactory behavior and learning. The extensive toolbox that Drosophila offers will aid in creating a tangible picture of how neuromodulation affects metabolism, olfaction, adaptive behavior, and brain functions general grasp [10].

So taking all these facts in consideration, we conducted this study to review and compile the available Drosophila models to study neuromodulator therapeutic interventions.

METHODOLOGY

Up until December 2022, published publications were retrieved using a variety of popular databases, including Google Scholar, SciFinder, MEDLINE, EMBASE, PubMed, Scopus, and Science Direct. We searched and extracted published material using the keywords "neuromodulation", "Drosophila", "neurotransmitter", "Dopamine", "octopamine", and "neuropeptide" pertaining to Drosophila models used to explore Neuromodulator activity. Searches restricted only to be conducted in English.

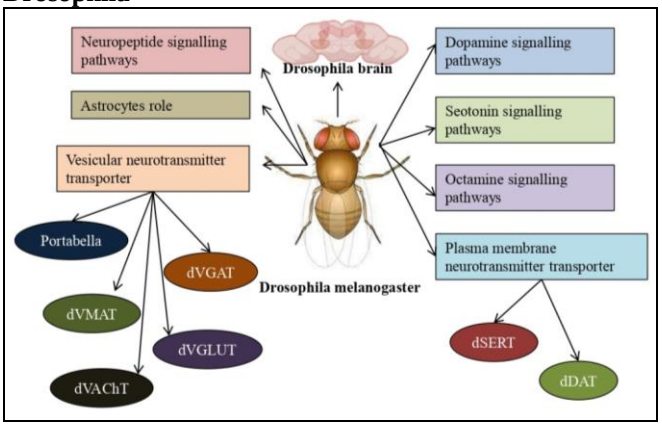
RESULTS

Neuromodulators have the power to quickly change the functional output of motor circuits, especially the tiny biogenic amine neurotransmitters. Here, we go over the neurotransmitter systems that Drosophila can be used to study (**Figure 1**).

Dopamine

Dopamine (catecholamine neurotransmitter) is an important neurotransmitter in animals that aids in motivation, reward, addiction, learning, and memory. Dopamine signaling changes have been linked to a variety of neurologic and psychiatric illnesses in people. Similarly, various behavioral flaws have also been linked to Dopamine signaling deficiencies in the Drosophila melanogaster. Drosophila is an effective genetic model organism to study the control of Dopamine signaling in vivo since the majority of the Dopamine involving gene production, secretion, transport, and signaling are conserved between species. Using more sophisticated genetic, electrophysiologic, imaging and pharmacologic methods in Drosophila, it will probably be able to identify the genes and neural circuits that control such behaviors [11, 12].

Figure 1: Neurotransmitters that can be studied in Drosophila



It is known that Parkinson's disease is a neurodegenerative disease characterized by hypokinetic and hyperkinetic movements, cognitive/behavioral abnormalities and sleep problems. The primary abnormality of Parkinson's disease is the loss of dopaminergic (DArgic) neurons. A lack of Dopamine signaling has also been linked to inherited dystonias, hypersomnia, restless legs syndrome, and periodic limb movement disorder, as well as mood disorders [13].

There is a progressive degradation of the dopaminergic nigrostriatal pathway in Parkinson's disease, resulting in postural instability, rigidity, and resting tremors. The Drosophila melanogaster can be used to imitate many elements of Parkinson's disease, such as the genetic deletion of neuronal dopamine production or degeneration of dopaminergic neurons induced by α-synuclein. By deficiency of dopamine, increased levels of 5-HT and arborizations in particular brain regions are also induced. The observed changes in 5-HT neuron plasticity suggest that the behavioral abnormalities seen in Parkinson's disease-related Drosophila models involve changes in 5-HT circuitry as well as Dopamine signaling loss, rather than just one or the other [14]. A study was done on the well-known insecticide rotenone (ROT), which is used in agriculture because it is inexpensive and works quickly. Additionally, models of Parkinson's disease in animals have been established using this technique. Against neurotoxicity induced by ROT in Drosophila melanogaster, Low Molecular Weight Chitosan (LMWC) was examined. LMWC (5 & 10 mg/mL in basal medium) was administered to male adult flies of 8–10 days old over a 7-day

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experiment to ROT induce neurotoxicity flies. Afterward, neurodegenerative and behavioral markers were evaluated. Therefore, in open-field and negative geotaxis investigations, flies exposed to only ROT had less locomotor behavior and had a higher mortality rate than the control group. In the fly head and body, ROT caused a drop in dopamine levels, a rise in reactive oxygen species (ROS), and cholinergic activity suggesting that ROT might cause oxidative stress. A co-exposure to LMWC reversed locomotor impairment, exploratory impairment, and biochemical parameter alterations induced by ROT, resulting in a 16-day survival rate. Parkinson's disease is effectively treated and managed using LMWC as a neuromodulator, according to the study [15].

Octopamine

The neurotransmitter, modulator, and hormone octopamine has been postulated to play a range of physiological roles in invertebrates. The Drosophila melanogaster, which offers a great system for genetic and molecular research of neuroactive chemicals, has been used in various models of octopamine. Using an antiserum specific to octopamine, the distribution of octopamine immunoreactivity was initially investigated. While brain lobes lacked immunoreactive somata, the larval octopamine neuronal pattern consisted of conspicuous neurons along the ventral ganglion's midline. However, both the ventral ganglia and the cerebral lobes displayed strong immunoreactive neuropil. It is believed that the larval body wall muscles were innervated by peripheral fibers that were transmitted by immunoreactive neurons. Octopamine has been linked to both central and peripheral brain processes in a number of insect species. It promotes flight motor activity, activates the firefly light organ, and modulates neurotransmitter activity in the locust central nervous system [16].

Although it is a basic activity, regulation and function of sleep are still poorly understood. The genetic and molecular factors underlying sleep and wakefulness can be addressed using the Drosophila model for sleep, which offers a strong system. Octopamine, a biogenic amine found in Drosophila, is an effective wake-promoting signal. Mutations in the octopamine production pathways results in increased sleep, which can be pharmacologically reversed by the octopamine administration. Additionally, electrically activating these neurons increased wakefulness compared to electrically silencing these neurons, which produce octopamine [17].

Function of protein kinase A (PKA), which is thought to be a possible target of octopamine signaling and is also involved in Drosophila sleep. Octopamine's ability to promote flies wakefulness was rendered insensitive by decreasing PKA activity among neurons. However, the mushroom bodies, a location previously connected to PKA impact on sleep, did not experience this PKA effect. These investigations pinpoint a brand-new route that controls sleep in Drosophila [18].

According to a study, octopamine released from a group of neurons, not acetylcholine, serves as a positive reinforcer for a single food odor source, leading to attraction. A subset of these neurons that are activated results in aversion, which is the opposite behavior. This aversion is caused by the release of octopamine rather than tyramine because it is suppressed in Tyramine-hydroxylase mutants (Tβh) lacking octopamine. The activation of the octopaminergic neurotransmitter system changes the attractiveness for an ethanol-containing food odor to a less appetizing food odor when given the choice between two sources of attractive food odor. The failure of Tβh mutants to change their attraction is consistent with the octopamine requirement in biassing the behavioral outcome. Octopamine is not necessary for attraction to occur; instead, the behavior or behavioral reaction must be initiated. Octopamine plays a role in the attraction to ethanol, in Tβh mutants, octopamine signaling is pharmacologically boosted to make alcohol more seductive, while octopamine receptor function is inhibited to make alcohol less seductive. When taken as a whole, octopamine in the central brain orchestrates behavioral outcomes by swaying an animal's preference towards the smell of food. This discovery might reveal a fundamental idea about how octopamine controls behavior in the brain [18].

Together, these findings provide a quantitative behavioral model to study the CNS's control of energy balance and a conserved neural substrate reveal that connects state of organismal metabolic to a particular behavioral output [19].

Neuropeptide

Studies of neuropeptide and peptide hormone signaling in Drosophila are maturing as a result of quick advancements in molecular genetics techniques that get over the limitations imposed by the fly's small size. Additionally, we have expanding peptidomics data sets and genome-wide knowledge of the genes implicated in peptide signaling. Numerous distinct neuropeptides have been found in a wide range of different neuron types in various regions of the Drosophila nervous system as well as cells in other places. Peptidergic signaling in the nervous system of the Drosophila fly, particularly how peptides control physiology and behavior both throughout development and in the fully grown fly. Peptide signaling functions both physiologically and behaviorally in Drosophila. Regulation of development, eating, growth, metabolism, homeostasis, reproduction, and lifespan are among these processes, as well as neuromodulation of learning and memory, olfaction, and locomotor control. The substrate of this signaling is the peptide products of around 42 precursor genes, which are synthesized in diverse combinations in distinct brain circuits or serve as circulating hormones. Drosophila, there are about 45 G-protein-coupled peptide receptors that have been discovered, and most of these have ligands. The range of roles neuropeptides and peptide hormones play in a fly's daily existence is still poorly known, and certain peptides have more specific functions than others [20].

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Aggressive behavior is regulated by a variety of neuromodulators, including neuropeptides and biogenic amines. In Drosophila melanogaster, the neuropeptide drosulfakinin (Dsk) regulates aggression. Dsk or the CCKLR-17D1 deletion of the Dsk receptor reduced aggression. Dsk-expressing neurons were activated and inactivated to cause and prevent male aggression, respectively. Furthermore, it has been demonstrated using transsynaptic tracing, electrophysiological analysis, and behavioral epistasis that Dsk-expressing neurons operate as downstream effectors of a subpopulation of P1 neurons (P1a-splitGAL4) to regulate aggressive behavior. Additionally, winners have increased calcium activity in Dsk-expressing neurons. The promotion of social dominance by conditional Dsk overexpression suggests a connection between Dsk signaling and favorable consequences [21].

Astrocytes

The astrocytes that are connected to synapses all across the brain express neurotransmitter receptors that can raise intracellular calcium (Ca2+). Although it has been suggested that astrocyte Ca2+ signaling can modify the activity of neuronal circuits, the pathways governing these processes are poorly understood, and there is scant in vivo data connecting variations in astrocyte Ca2+ to changes in neurotransmission or behavior. According to certain research, in vivo Ca2+ signaling processes in Drosophila astrocytes are activity-regulated. Through the Octopamine-tyramine receptor (Oct-TyrR) and the TRP channel Waterwitch (Wtrw), Tyr and Octopamine, which are produced by Tdc2+ neurons, encourage Ca2+ increases in astrocytes, and astrocytes in turn affect downstream dopaminergic neurons. Dopaminergic neurons were muted when Tyr or Octopamine was applied to live preparations; this suppression required astrocytic Oct-TyrR and Wtrw. Increased astrocyte Ca2+ signaling, which was mediated by astrocyte endocytic activity and adenosine receptors, suppressed dopamine neuron activity. Odor-driven chemotaxis behavior and touch-induced startle responses were significantly affected when Oct-TyrR or Wtrw expression was specifically disrupted in astrocytes. Our research establishes Oct-TyrR and Wtrw as critical elements of the astrocyte Ca2+ signaling machinery, shows that astrocytes can mediate Oct- and Tyr-based neuromodulation, and shows that astrocytes are required for a variety of sensory-driven behaviors [22-25].

Although astrocytes influence a number of crucial elements of brain homeostasis, their function in sleep was completely unknown until recently. Throughout the sleep-wake cycle, astrocyte activity fluctuates dynamically, and alterations in intracellular signaling pathways may be used to encode the need for sleep. Additionally, astrocytes exocytose or produce sleep-inducing chemicals that affect the control of sleep, sleep architecture, and brain activity. Numerous findings from Drosophila melanogaster suggest that astroglial sleep processes are constant throughout evolution [26].

The use of astrocytes in mechanistic, theoretical, and computational research of brain circuits offers new perspectives on behavior, its regulation, and its manifestations in disease [26].

5-HT pathway

5-HT and other biogenic amines play a role in associative learning. Changes in memory performance with modifying either of these signals are indicative of this function. It is either unclear or debatable how the serotonergic system contributes to the reinforcement of insect associative learning. However, there is evidence that 5-HT is necessary for place memory, which is disproven by genetically altering 5-HT levels and employing pharmaceutical treatments. As a result, 5-HT may be consider essential for an insect's ability to build memories [27].

To control various facets of the animal behavior, 5-HT binds to distinct ligand-gated ion and G protein-coupled receptors. Along with many other insects, Drosophila regulates both feeding and movement. The larval Drosophila has evolved as a helpful model for investigating the molecular and anatomical underpinnings of behaviors (chemosensory) due to its genetic adaptability and neural simplicity. This is especially true for the system of olfactory, which is largely detailed over the first 3 tiers of information regarding neurons processing down to the synapse level. According to research, 5-HT signaling is involved in memory and learning of Drosophila larvae. In the long run, findings of these studies might reveal aspects of reinforcement processing that are developmental, 5-HT dependent, and possibly shared with adult Drosophila [28].

Millions of people suffer from Major depressive disorder (MDD), although the pathogenesis is poorly understood. To create rodent models that mimic the symptoms like depression, such as anhedonia, and general lethargy, researchers have used either unavoidable punishment (learned helplessness) or prolonged mild stress like vibration-stress strategy that lowers the voluntary behavioral activity of Drosophila. Treatment with lithium chloride decrease depressive-like condition among flies, much like it does in many MDD patients. Feeding the antidepressant 5-hydroxy-L-tryptophan or sucrose, which raises 5-HT levels in the brain, can alleviate the behavioral abnormalities, which are correlated with lower 5-HT production at the mushroom body. 5-HT-1A receptors in the mushroom body's α-/β-lobes facilitate this alleviation, whereas 5-HT-1B receptors in the γ-lobes regulate behavioral inactivity. The key function of 5-HT in controlling stress responses in flies and mammals points to evolutionary conserved pathways that can serve as targets for therapy and methods to promote resilience [29,30].

NEUROTRANSMITTER TRANSPORTERS

Neurotransmitter transporters carry traditional neurotransmitters such as the biogenic amines and acetylcholine as well as the glutamate, amino acid neurotransmitters GABA, and glycine across biological membranes. There are two separate functions represented by

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plasma and vesicular membrane neurotransmitter transporters. Plasma membrane neurotransmitter transporters, which also recycle neurotransmitters once they have been released, prevent synaptic transmission [31]. Additionally, vesicular neurotransmitter transporters, which are found on the membranes of secretory vesicles, are responsible for storing and transporting neurotransmitters into the vesicle lumen [31]. Large dense core vesicles (LDCVs), which also store and release peptide neurotransmitters, as well as synaptic vesicles (SVs), require vesicular transporters for the storage of neurotransmitters [32]. Vesicular transporters do not, however, pack peptides into the lumen of LDCVs; rather, they do so while the vesicle is being generated [33]. Additionally, peptides do not go through plasma membrane transfer. Similar to this, "novel" neurotransmitters like nitrous oxide do not need particular transport proteins because they can be synthesized on its demand and can pass quite easily through lipid membrane barriers [34]. It is still not known if lipid-based signaling chemicals like anandamide need particular transporters to penetrate biological membranes [35].

To find novel compounds that could enhance the performance of neurotransmitter transporters, this *in vivo* tools are useful. Drugs that would enhance signaling in the octopaminergic circuit necessary for the larvae's natural movement can be tested in larvae. The outcomes of this screening produced a number of compounds that, by definition, would not be aminergic medicines and are unlikely to directly bind dVMAT. In the fly, screening for genes and medications that alter transport function is achievable. [35].

Vesicular Neurotransmitter Transporters

a) dVAChT

Research report that, the fly's dVAChT was a first vesicular neurotransmitter transporter that is molecularly characterized. One of the dVAChT mutants is the weaker allele dVAChT2, which survives the second larval stage but moves more slowly than wild type animals. DVAChT1 is embryonic fatal [36].

b) dVGLUT

Biochemical studies revealed the fly had vesicular glutamate transport activity before it was molecularly characterized. Unlike mammals, which have 3 unique VGLUT genes, Drosophila carries only dVGLUT (a single VGLUT ortholog,). All glutamatergic neurons in the adult fly and larva, as well as the glutamatergic motoneurons that innervate the larval NMJ, express dVGLUT [37].

c) dVMAT

Fly genomes only contain one VMAT gene, in comparison to the human genome's which have two unique VMAT genes. The 12 anticipated transmembrane domains, which are most likely to be in charge of substrate recognition and transport, share similar fundamental structures between dVMAT and mammalian VMATs. In fact, the relative affinity and neurotransmitter substrate selectivity of dVMATs are often similar to those of mammalian VMATs. For instance, reserpine inhibits dVMAT at sub-micromolar doses [38,39].

d) dVGAT

The genome of Drosophila has only one vesicular GABA transporter gene (dVGAT), just like in mammals. dVGAT appears to be expressed in all GABAergic neurons in the larva since it precisely co-localizes with GABA in the ventral nerve cord and is found in the majority, if not all, adult GABAergic neurons. It's unknown whether Drosophila use glycine as a neurotransmitter in the same way as mammals do, and whether dVGAT can store glycine as well [40,41].

e) Portabella

A second vesicular transporter, portabella, that appears to be missing from mammalian genomes, is expressed by Drosophila and several other insects. According to studies, the gene's name was chosen because of its strong expression in MBs. Prt is expressed in the Kenyon cells (KCs), which are the intrinsic neurons of the MBs. Unexpectedly, it is unknown what neurotransmitter KCs store and release. Although prt's core structure is most comparable to that of DVMAT and it is possible that the substrate is similar to known monoamines, prt may transport a novel neurotransmitter even if the biosynthetic enzymes for Dopamine, 5HT, octopamine, and histamine are not present in KCs. [42,43]

Plasma membrane transporters

a) dSERT

The plasma membrane neurotransmitter transporter which was firstly discovered in flies was Drosophila serotonin transporter (dSERT) [44]. According to this research, the substrate specificity of dSERT deviated from that of its mammalian orthologs, including a reduced affinity for certain antidepressants like citalopram but a larger affinity for the mammalian DAT antagonist mazindol. In comparison to hSERT, transport via dSERT also seemed to have a less strict demand for chloride [45] claimed that cocaine had a much higher affinity for dSERT than for hSERT, although similar affinities for both orthologs were found [45].

b) dDAT

Through homology-based cloning, the Drosophila dopamine transporter (dDAT) was discovered. Its kinetic profile is comparable to that of hDAT. According to in situ hybridization studies, dDAT expression in larvae matched the pattern for Dopamine neurons that had previously been identified. Although not all known Dopamine cells were detectably labelled, in situ images of adult heads partially match the localization of Dopamine cells. Northern blots demonstrate a single mRNA species of 3–4 kB. dDAT-mediated transport, like all other DAT orthologs, is sodium dependent and capable of supporting both efflux and sodium-coupled transport. However, research has demonstrated that cocaine inhibits dDAT, which lengthens Dopamine uptake in vivo. This suggests that dDAT is likely necessary for at least some of the behavioral effects of cocaine [46,47].

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CONCLUSION

Numerous behavioral circuits involve neuromodulation as a key regulatory component, and modulators' reconfiguration of these circuits can have both long- and short-term effects. Neuromodulatory systems have recently been demonstrated to have a significant role in the control of sleep and other behaviors in Drosophila melanogaster, an organism that has emerged as a key model system for molecular and genetic studying of behavior. The fly is a system that is well-positioned to shed fresh light on the challenging problem of how neuromodulation might connect situation-specific behavioral demands with the brain's arousal state. The fly has increasingly well-defined behavioral circuitry and potent genetic tools.

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CONFLICT OF INTEREST

Authors do not have any conflict of interest.

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ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

DATA AVAILABILITY

The data used in the current study is available from the corresponding author on reasonable request.

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