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A Review: *Drosophila melanogaster* as A Model Organism to Study Memory

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ABSTRACT: The purpose of the article is to show *Drosophila melanogaster* as a model organism in studying and understanding memory. We had covered types of memory, an aspect that affects & nourishes the memory and its consequences along with the pathways. In this we explored how circadian rhythm, ageing, sleep deprivation, oxidative stress, and alcohol (ethanol) consumption affect memory and how neurodegenerative diseases leads to disruption of different types of memory in *Drosophila*. Also factors studied in this article may show similar effects on human as 75% of genes responsible for human diseases have homologs in flies.

KEYWORDS: - *Drosophila Melanogaster*, Memory, Sleep, Circadian Rhythm.

I. INTRODUCTION

“The power of the mind to remember things” or “something remembered from the past like a recollection”, these several interrelated ideas denotes term memory. It refers to the processes that are used to acquire, store, retain, and later retrieve information. Encoding, storage, and retrieval are three major processes involved in memory.

Short term memory (STM), long term memory (LTM) and middle term memory (MTM) are the three parts of memory in *Drosophila*. Short-term memory also known as working memory allows recall for a period of several seconds to a minute without rehearsal. Its capacity is very limited. STM temporarily records the succession of events in our lives. Short-term memory has a storage capacity of only about seven items and lasts only a few dozen seconds. It may register a face that we see in the street, or a telephone number that we overhear someone giving out, but this information will quickly disappear forever unless we make a conscious effort to retain it. STM includes: sensory memories, short term storage, working memory, long term working memory.

Much larger quantities of information for potentially unlimited duration (sometimes a whole life span) can be store in long-term memory (LTM). It lets us retain the meanings of words and the physical skills that we have learned. LTM stores all the significant events that mark our lives. Its capacity seems unlimited, and it can last days, months, years, or even an entire lifetime! But it is far from infallible. It includes: olfactory, visual, explicit, Middle term memory (MTM) lies between STM and LTM containing anesthesia resistant memory (ARM) and anesthesia sensitive memory (ASM) (1).

II. FACTORS AFFECTING MEMORY OF *DROSOPHILA*

Factors that affect different types of memory and its function either directly or indirectly in *Drosophila* are listed below.

Circadian Rhythm:

Circadian rhythms are a series of endogenous autonomous oscillators generated by the molecular circadian clock which acting on co-ordinating internal time with the external environment in a 24 hour daily cycle. It is a natural cycle of physical, mental and behaviour changes that the body goes through a 24 hour cycle. *Drosophila* circadian rhythm have paved the way for understanding circadian behaviour and diseases related to sleep-wake condition in other animals, including humans. Abnormal circadian rhythms may be uplinked to obesity, diabetes, depression, bipolar disorder,

seasonal affective disorder, and sleep disorders such as insomnia. Circadian rhythm is sometimes called the body’s clock. It reflects direct response to the changing temperature or light. *Drosophila melanogaster* (fruit fly) shows many different and easily in large scale measurable circadian patterns of behaviour than any other model organisms. Also, it has the reduced gene number that means there is less redundancy & less compensation and its genome is the closest to that of mammals.

Drosophila for instance is only active when it is not too hot and dry on the one hand & when it’s not too cold on the other hand. Fruit flies hatch in greatest numbers just at dawn. *Drosophila melanogaster* shows two activity peaks – one in a morning and one in the evening. It also shows other clock related behaviour that is eclosion, olfactory sensitivity, egg laying, courtship, gustatory sensitivity or learning and memory, especially the simplicity of its neuronal network organizations (4). About 150 clock cells per brain hemisphere are yet manageable and permit dissection of the function of single cells or cell clusters in the brain. The late Seymour Benzer in early 1970s revealed 'clock gene' in which he discovered abnormal circadian behaviour. The gene responsible for the same is located on X-chromosome (2). To adapt to different environments and photoperiods, circadian clock need to be flexible, otherwise it would lack an important ability. Therefore, circadian clock evolved sophisticated molecular mechanisms to react to new environments. Some input factors called ‘Zeitgebers’ harmonize clock neurons to environmental light, temperature, social cues or even magnetism influences circadian rhythm. Light is the most important input factor. The response to variable light is mainly caused by degradation of Tim protein (6).

In *Drosophila*, as there are two circadian oscillator i.e. the morning oscillator which accelerates by light and evening oscillator which shows inducing activity in evening and is slowed down by light. Both oscillators are coupled. The reason for this bimodal activity is the adaptation to different photoperiods. Molecular genetic analysis has made circadian rhythms in *Drosophila* one of the best understood behaviours at molecular level.

The Circadian Clock in *Drosophila*:- A number of genes in *Drosophila* are turned on when the animal is exposed to light:

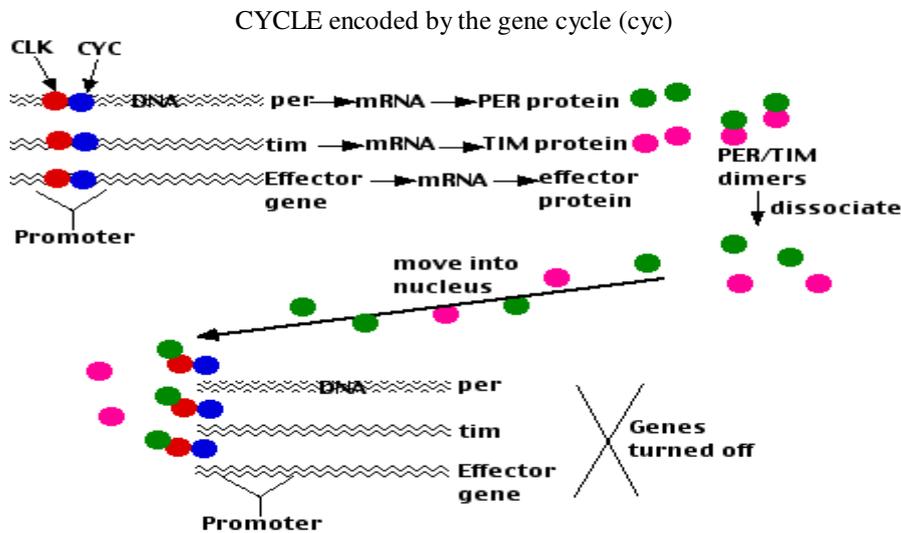
- 1) Effector genes whose products mediate the animal’s responses (e.g. hatching or molting)
- 2) Clock genes whose products regulate the circadian clock

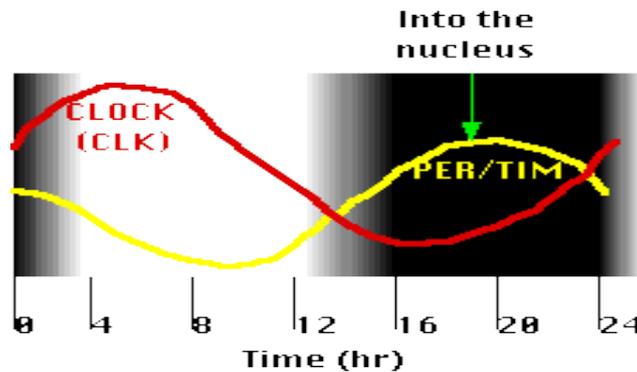
Two key members of this group are: Period (per) & Timeless (Tim)

Activation of all of these genes requires that their promoters are bound by the protein transcription factors (3).

CLOCK encoded by the gene clock (clk)

The Mechanism:





The PER and TIM proteins (synthesized on ribosomes in the cytoplasm) form dimers. When the concentration of these gets high enough (early evening), they dissociate and are transported into the nucleus (3).

Here PER Binds to the CLK/CYC transcription factors, removing them from the promoters of the genes they activate; thus shutting off transcription. Because these genes include PER and TIM, the result is a negative feedback loop; that is, the product of the PER gene inhibit its own synthesis (as well as that of TIM). Just as the heat of a furnace turns through the thermostat – its own production off, so a rising level of PER/TIM dimers turns off further synthesis of them. As the level then falls, this inhibition is lifted and PER/TIM activity begins anew to turn on clock gene expression. The time required for the different effects results in the levels of PER/TIM and CLOCK oscillating in opposite phases with a circadian (~24 hr) rhythm (3).

Setting the Clock:-

Even without any external cues (e.g., alternating light and dark), the cycles persist although they tend to drift away from environmental time. The clocks are precise under natural conditions light is one of the most important because they are "set" (synchronized) by environmental cues. The protein cryptochrome (CRY) absorbs blue light in *Drosophila*. This causes an allosteric change in its conformation enabling it to bind to TIM and PER. this causes to break down (in proteasomes) TIM and PER ending their inhibition of gene transcription.. If this happens when PER/TIM levels are rising (late in the day), it sets the clock back. But if it happens when PER/TIM levels are declining (late in the night), it sets the clock ahead (3).

Circadian Rhythm Disorder:-

Impairment in normal rhythmicity favors the activation of gene expression and pro-inflammatory responses, which may play a role in neurodegeneration. Through the modulation of oxidative stress responses a proposed pathway associates the master clock to neurodegeneration. However other mechanisms such as neuroinflammation or an impaired degradation of pathogenic protein aggregates might also be involved. There are some evidences of a link between circadian system and psychiatric diseases. Environmental or genetic disruption of the circadian system leads to an increased liability to psychiatric disease. Disruption of clock genes or clock network might be related to etiology of these pathologies. Through clock-independent pleiotropy some genes known for their circadian clock functions might be associated to mental illness. In Psychiatric patients, sleep and memory are often impaired. A majority of patients with schizophrenia, bipolar and depressive disorders refer sleep disturbances (insomnia or sleepiness). They may also be characterized by impairments in the selection of positive or negative information from working memory and in their capability to access episodic memories. In addition, patients may also display impairments in interpersonal interactions. Several data suggests an involvement of circadian clock or genes in determination of these complex behaviours can also be seen in *Drosophila* (5). Circadian rhythm clocks participate in regulation of neurogenesis. Higher incidences of brain diseases such as sleep disorder and depression were observed in a population with interrupted circadian rhythm. People suffering from psychiatric disorders can induce emotional & psychotic attacks in individuals through circadian dysregulation. Most of the researchers suggest that circadian disorder is a symptom of neurodegenerative diseases including Alzheimer's, Parkinson's and Huntington's disease (8). The impairment formation of memories and manifestation of other cognitive deficits are due to disruptions in circadian regulation. Circadian dysfunction markedly affects cognitive functions (7).

The *Drosophila* and Mammalia circadian oscillator are comparable and many components are evolutionary related. Also, it has complex nervous system which resembles much with the cell and neurobiological level with humans. Many neuropsychiatric diseases can be studied and understood well by using *Drosophila melanogaster* as a model. Hence, *Drosophila* might be informative in the study of possible relationship between circadian clock and human psychiatric diseases. The complex behaviour such as sleep as well as memory appears to be influenced in some way by circadian system or gene, even if the mechanistic relationship is still unclear. That is why this area of research has to be explored more in future to get a clearer picture.

Sleep:

For performing several brain functions and maintaining memory sleep is very crucial and it promotes consolidation of memory. Irregular cycle of sleep can impair memory be it directly or indirectly. Sleep is interrelated to many of the brain functions and it is regulated by the circadian clock, which ensures appropriate timing of sleep, but the amount and quality of sleep are also determined by other mechanisms that ensure a homeostatic balance between sleep and wake. Sleep is also regulated by factors such as food availability, stress, and social environment.

In *Drosophila*, memory formation is regulated in circadian manner. Circadian clock modulates short-term olfactory memory peak memory levels in early to mid-evening & lowest memory levels during mid-day in both light-dark cycles (LD) and constant darkness. Circadian mutants for core clock genes; period (PER) & timeless (TIM) failed to show any rhythms in short-term memory (STM). Circadian rhythm in STM appears to be modulated by central brain circadian oscillators and not the peripheral circadian clock in the antennae as cryptochrome mutants exhibited strong circadian rhythms in STM (3). Sleep is important for optimal cognitive performance, and sleep disruptions lead to defects in learning and memory. It is said that enhanced amount of sleep can reverse memory meaning if the sleep cycle is disturbed it may lead to memory loss.

Sleep Deprivation:

If you don't get enough sleep a condition occurs termed as sleep deprivation. Sleep deficiency is a broader concept. It occurs if you don't get enough sleep due to any medical or other reasons. Sleep plays a key role in learning and memory in Human and other vertebrate. Because of sleep deprivation hippocampal plasticity is seen, it's result in impaired subsequent retention. In *Drosophila* loss of sleep caused learning and memory impairment. It also affect waking experience in *Drosophila*, All these studies shows that sufficient sleep is very important in learning and memory. Several experiments are carried out for study the impact of sleep deprivation on memory and learning.

To study the impact of sleep deprivation on memory and learning, sleep deprivation experiment performed to show that how flies silence transmission of mushroom bodies in brain due to that for some hour memory in *Drosophila* get impaired. 1day sleep deprivation effect of slpD on learning and memory was evaluated using Pavlovian olfactory conditioning in *Drosophila* and its locomotor activity was measured, using *Drosophila* activity monitoring system in 12:12 light dark cycle. And it shows that slpD specifically impaired 1 hour memory in wild type canton's flies, and the effect remain at least for 2 hours. Mechanisms studies shows that flies with either silence transmission of mushroom bodies (MB) during slpD or down regulate the level of cAMP in the MB demonstrate no slpD induced 1 hour memory impairment and results show that slpD specifically impaired 1 hour memory in *Drosophila* and either silencing of MB transmission during slpD or down regulating of the cAMP level in the MB protect the flies from slpD induced impairment (9). Due to sleep deprivation in major depressive disorders working memory and learning, sleep get affected. In deprivation disorders 2-pore domain potassium channel TREK-1 play major role and its relation with sleep and memory were shown in the following experiment.

In major depressive disorder (MDDs), sleep and cognitive dysfunction are common. Recently, the 2-pore domain potassium channel twik-related K (+) channel 1 (TREK-1) has been identified to be closely related to the etiology of MDD Function of TREK-1 is still unknown either is involved in the regulation of sleep and cognition. For this one more experiment was carried out to study the role of outwardly rectifying K+ channel-1 (ORK1) (TREK-1 homolog in *Drosophila*) in sleep and cognition in *Drosophila*. The mutant and over-expressed lines of ork1 were generated using *Drosophila* genetics. To test sleep time and short-term memory of the mutant and over-expressed ORK1 lines, Sleep analysis and short-term memory experiments were used. Result showed that the learning index of ork1 mutant lines was increased compared to wild type. Ork1 mutant could obviously decrease sleep time in *Drosophila*. They also found that ORK1 over-expression could increase sleep time and decrease learning index in *Drosophila*, contrary to the ork1 mutant lines. This study suggests that ORK1 might play an important role in the regulation of sleep time and short-term memory in *Drosophila* (10). This studies show that sleep deprivation majorly affect short term memory in *Drosophila*.

Aging:

Aging could be a phenomenon which is related to functional senescence in most organisms. *Drosophila melanogaster* has short life span and numerous age-related functional senescence similarities with human subjects (11). *Drosophila melanogaster* is useful model for studying the normal aging process and its associated cognitive changes, and cause disturbance in memory, sleep, locomotion and other behaviours in aging flies (12). Decline in cognitive function in old flies with respect to both short lived and consolidated form of olfactory memory. During aging memory impairment is to decline in neuronal function and increase in neurodegeneration (11). Flies had long, uninterrupted bouts of sleep when they were young sleep become fragmented as they aged (13). Young flies were able to fully restore the stable memory for 3 hours. Post extinction while aging flies were failed to do so. Only stable but not the labile memory component was suppressed by extinction results in higher memory loss in aging flies. Young flies restored memory reduction while it lacks in aging flies (14). Age related defect in olfactory memory is identical to those of MTM mutant amnesiac (Amn). Aging may also affect motor activity. Aging is known to be associated with a decrease of learning and memory. Some regions of the brain are more sensitive to aging than others. ARM is less sensitive to aging as LTM formation is highly sensitive (16). LTM that is independent of protein synthesis remain unaffected by age, whereas that form of LTM requiring protein synthesis become impaired therefore there is mechanistic specificity in effect of aging on LTM. Aging disrupts specific temporal form of memory, including ITM (Intermediate Term Memory) and protein synthesis LTM, but not STM and protein synthesis independent LTM (17). An increase in oxidative stress disrupts sleep-wake cycle in a manner similar to that of aging as sleep become fragmented with age and rate at which this fragmentation occurs depends on ambient temperature and life span, it is an integral part of physiological aging process (13). There will be decrease in expression of ETC gene as well as increase in expression of immune and stress gene of all this been reported in aging studies. Co-expression module have been identified i.e., enriched in gene known to affect learning and memory in flies (12). Decreased IIS signalling promotes learning and has been implicated in memory and aging. TOR signalling blocks LTM and LTF while reduced TORC2 activity causes LTM deterioration. Dietary restrictions affects learning performance during aging as young DR flies show enhanced MTM but their STM is not affected while mid aged flies has poor STM that of flies grew on rich diet. Inhibition of cdk5 kinase decreases autophagy causes defect in brain regions associated with olfactory learning and memory (18).

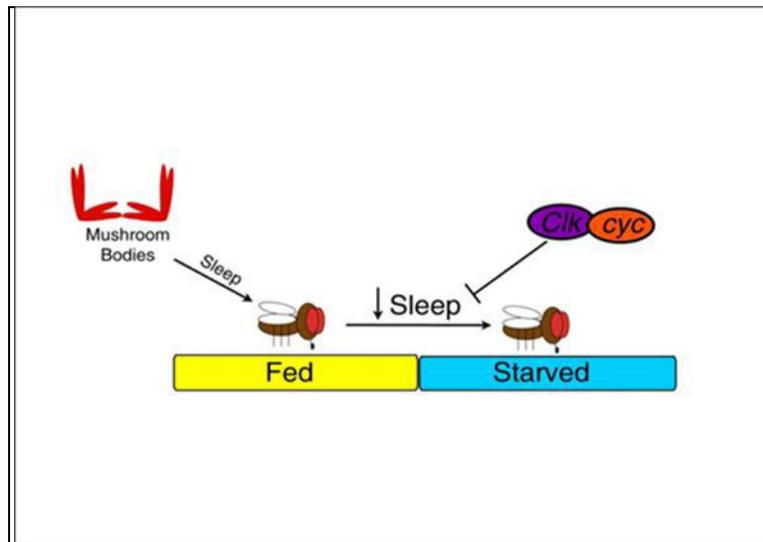
Starvation:

Starvation is the result of a severe or total lack of nutrients needed for the maintenance of life. *Drosophila melanogaster* is model organism that is straightforward for studying a number of biological investigations including feeding behaviours under various conditions. *Drosophila* is considered as an herbivore, At times, *Drosophila* larvae may encounter nutritional stress that could be transient or chronic and therefore must learn to adapt to it for survival (19). Experiments have been done to find out the survival response of *Drosophila* under starved conditions, which resulted in finding out that under resource shortage in order to survive starvation the brain prioritizes the activation of only the crucial mechanisms of the body and has been found to shut down the long term memory (LTM) in order to save the energy.

Brain uses almost 20% of body energy which is known for regulating the energy equilibrium in the body. Studies show that when *Drosophila* is kept under the situation of starvation it shuts down the long term memory (LTM) but keeps the anesthesia resistant memory (ARM) functioning, to save the energy (22). Why so? It's because the long term memory (LTM) forms through the de novo protein synthesis which requires metabolic machinery and will lead to huge amount of energy. Consumption and under the condition of food deprivation it will not be possible for the body to generate that much amount of energy. Thus in contrast it activates the anesthesia-resistant memory (ARM) a memory process which results in the formation of consolidated memory resistant to disruption of the patterned activity of the brain, without requiring protein synthesis which will save a lot amount of energy and prevent non vital energy expenses also will help an organism to survive under the severe food deprivation conditions. Researchers have also experimented forcing the long term memory (LTM) on *Drosophila* instead of anesthesia resistant memory (ARM) but that resulted in death of an organism, thus it shows that starvation can affect the memory of a *Drosophila*.

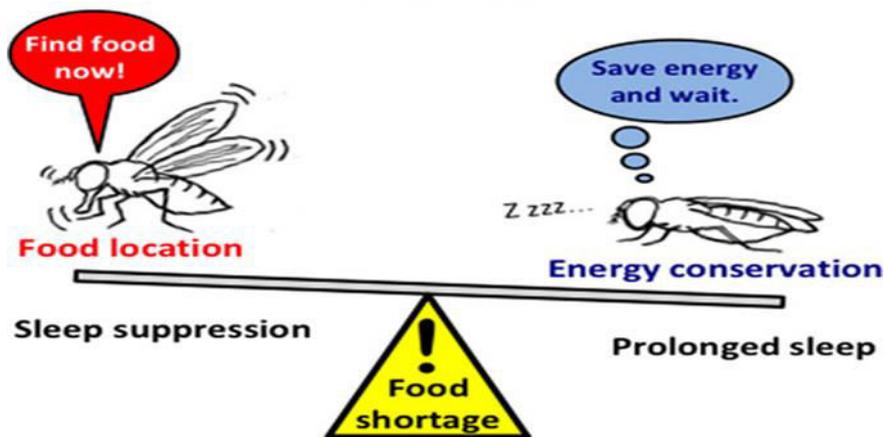
Another studies show that starvation in *Drosophila* induces sleep loss in them, that means starvation suppresses sleep. This sleep insufficiency or sleeplessness signal towards sleep deprivation which is known to impair learning and memory in *Drosophila* (20). As mentioned above that starvation induces sleep loss in *Drosophila* that sleep suppression is done by the circadian clock genes Clock (Clk) and cycle (cyc). These both are critical for proper sleep suppression during starvation. Studies suggest that the homeostatic regulation of feeding and sleep involves functionally interconnected mechanisms. To determine whether flies suppress sleep during starvation, they measured

their locomotor activity in the *Drosophila* activity monitor system (DAMS) and analysed sleep. They monitored changes in sleep during 24 hr. of food deprivation and found that similar to mammals, both male flies dramatically suppressed their sleep during starvation compared to control flies fed ad libitum. Determining the percentage change in sleep within individual animals revealed that starved flies robustly suppressed sleep compared to baseline control levels. Flies housed with sucrose did not suppress their sleep, indicating that caloric intake with no amino acids is sufficient to support normal levels of sleep. Flies housed with the nonmetabolizable sweetener sucralose suppressed sleep confirming that the effects of starvation on sleep are due to a caloric deficit rather than sensory systems detecting the absence of food in an environment.



Courtesy: Keene AC, Duboué ER, McDonald DM, Dus M, Suh GS, Waddell S, Blau J. Clock and cycle limit starvation-induced sleep loss in *Drosophila*. *Curr Biol.* 2010 Jul 13; 20(13):1209-15.

Fig: Clock and cycle Limit Starvation-Induced Sleep Loss in *Drosophila*



Courtesy: Miura, M, Takahashi, A. Starvation tolerance associated with prolonged sleep bouts upon starvation in a single natural population of *Drosophila melanogaster*. <https://doi.org/10.1111/jeb.13514>

Fig: Foraging strategy

Along with sleep suppression *Drosophila* (fruit flies) follows one more strategy to cope up with the situation of starvation which is called as foraging, foraging is a food seeking behaviour which animals possess when there is shortage of food, *Drosophila* tends to forage when they are starved (21). Foraging involves food searching behaviour that increases locomotor activity which results in sleep loss this shows that foraging also indirectly contributes in impairing memory.

Sleep suppression during starvation is a generalizable phenomenon in Drosophilidae; and observed it in multiple *D. melanogaster* laboratory lines and *Drosophila* species when tested with the same (20). Also foraging increases locomotor activity which adds in losing sleep. Thus this shows that starvation impacts memory in *Drosophila* by suppressing sleep which is known as cause of sleep deprivation.

Alcohol Induced Effects on Neurotransmitters in *Drosophila*:

To understand the behavioural responses of *Drosophila* to alcohol, the study of specific neurotransmitters could even be a critical topic. Neurotransmitters are both highly conserved from the mammal to the fly, which they're critically involved within the neurobiological activity of alcohol. Excitatory, inhibitory, or modulatory effects can be exerted by neurotransmitters. Flies and mammals share many conserved similarities but there are some differences between their neurotransmitter systems. In mammals, glutamate is primary excitatory neurotransmitter within the CNS which they use Acetylcholine (ACh) at synapse. Conversely, flies use glutamate at the synapse and their primary excitatory neurotransmitter is ACh (23). In vertebrates and flies, GABA and glycine both function as inhibitory neurotransmitters and thus the two classes of organisms also share many neuromodulators (24). In flies, neurotransmitters show an oversized form of behaviours impacted by alcohol, which are summarized in Table 1.

Sr. No.	Neurotransmitters	<i>Drosophila</i> behaviours impacted by alcohol
1	Dopamine	Associative learning (25), Sleep and arousal (26), Olfactory learning and memory (25)
2	Serotonin	Associative learning (27), Long-term memory formation (27), Sleep (28)
3	GABA	Associative olfactory learning (29), Sleep length and onset (30), Sleep and memory consolidation (31)
4	Acetylcholine	Sleep promotion (32)
5	Glutamate	Olfactory learning and memory (33), Wake promotion (34)

Table 1. *Drosophila* behaviours associated with each neurotransmitter

The fly brain and the mammalian brain do not show any structural resemblance but *Drosophila* has neural circuits which fulfil roles like those of the vertebrate brain. Like in mammals, alcohol impacts the *Drosophila* dopaminergic (DAergic system) (23) and plenty of DA-related behaviours are linked to and affected by alcohol. Several DA mediated behaviours in *Drosophila*, such as locomotion, sedation, and reward are affected by alcohol. Serotonin is critical for memory formation in *Drosophila* (27). Serotonin exerts behavioural and physiological effects on processes like sleep (28). GABA activity impacts numerous behaviours. In *Drosophila*, these behaviours include olfactory learning (29), and sleep regulation (42). In mammals; glutamatergic activation likely has circadian fluctuations (36) which is additionally true for flies. Reducing glutamatergic release from glutamatergic neurons decreased wakefulness, and increased glutamatergic activity promoted wakefulness (34). This implies that glutamate is wake-active in *Drosophila* (34).

Learning and Memory:

DA is incredibly important for complex behaviours like learning and memory. In *Drosophila*, blocking DA inhibits the acquisition of aversive memories (37). DAergic inputs to the Mushroom Body (MB) are vital for olfactory learning and memory. Serotonin affects numerous behaviours in *Drosophila*, and manipulation of the fly serotonergic system has recapitulated symptoms of neuropsychiatric disorders like depression and anxiety. Glutamate likely plays an awfully important role in the antennal lobe (AL). Both ionotropic and metabotropic glutamate receptors are present in the AL (33). Optogenetic studies indicate that the dorsal population of circadian clock neurons uses glutamate as an inhibitory transmitter to push sleep. Dopamine (DA) plays a dual role in learning and forgetting. Researchers propose that as dopamine neurons (DANs) provide unconditioned (US) signal to the MBs predominantly through the dopamine

receptor dDA1 and fulfil their role in the acquisition of memory, they still release dopamine onto the MBs that signals through the DAMB receptor to cause forgetting of recently acquired labile memories (38). Memory expression is enhanced by learning on blocking the output from DANs, while stimulating DANs accelerated memory decay. The dopamine-based forgetting mechanism preferentially removes labile memories, because a blockade of DAN synaptic activity enhances labile but not cold resistant, consolidated memories. Forgetting of consolidated memories can be induced due to excessive stimulation of the mechanism by Trp1. TrpA1-mediated stimulation results in overall higher levels of dopamine signalling that renders consolidated memory, formed for either aversive or appetitive conditioning, vulnerable to forgetting (38).

Neurodegenerative Disease:

Alzheimer's disease:

The most common hypothesis is the formation of beta amyloid plaque which leads to neurodegeneration. By the action of γ secretase & BACE1 (β -site APP cleaving enzyme-1) the intramembrane amyloid precursor protein APP (in *Drosophila* it is amyloid precursor protein-like (APPL)) get cleaved to generate $A\beta_{42}$ which is pathogenic while the α -secretase cleaves the APP in non- pathogenic manner (39) (40) (41). Amyloid aggregates generation also involves tau protein. Normally the tau proteins are bounded to microtubule but when it is hypo phosphorylated it get detached which destabilize the microtubule & decreases neurotransmission.

The models of Alzheimer's disease in *Drosophila* are basically divided into three groups. One is by mutation in *Drosophila* ortholog of human disease gene, models used for studying environmental stresses on toxicity of $A\beta$, transgenic constructs which carry alleles of human disease causing gene. The third category which uses transgenic constructs is also used to study tau involvement in Alzheimer's disease (42). *Drosophila* homolog of Alzheimer's disease revealed about human gene which functions in the pathways related to disease. The draper gene (MEGF10 in humans) functions in engulfment of $A\beta$ by glial cell which reduces neurotoxicity in Alzheimer's disease of *Drosophila* (55). Another study which includes nearly 87 *Drosophila* genes, all with homologs in human of which by genome wide association study it is found that nine genes impact more on toxicity of tau. Those 9 genes are XYLT1 (oxt), CELF1 (aret), PTPRD (Lar), CD2AP (cindr), ITGA9 (scb), FERMT2 (Fit 1, Fit 2), SNRPN (SmB), MAST4 (CG6498), ITGAM (scb) (56). The FERMT2 & CD2AP which is association with integrin plays role in cell adhesion. Also, ITGA9 7 & ITGAM generates α along with PTPRD & XYLT1 function in cell adhesion. (44) (45) (46) (47).

Lewy body dementia- Parkinson's disease:

In this disease the aggregation of α -synuclein occurs in brain cell because of which there is loss of posture stability, tremor due to degeneration of dopaminergic (DA) neurons in midbrain which help in transferring dopamine to basal ganglia. Other areas in brain like olfactory tubercle, cerebral cortex, post commissural putamen which leads to more different type of symptoms (48). Parkinson disease homolog gene is present in *Drosophila* which are LRRK2, PINK1, PARK2, UCH L1, HtrA2, Tau, GBA, DJ-1

In *Drosophila* model PINK 1 is very necessary for mitochondrial functioning, mutations in PINK 1 have less DA neurons so exhibit dysfunctions. The overexpression of DA neuron in *Drosophila* model shows caspase dependent death of imaginal disc in eye, disruption in patterning of pupal retina (49). Removal of HtrA2 which shows protease activity & associate with apoptosis can decrease the ommatidium number, motor ability & life span. (50). When the tau is overexpressed in mushroom body of *Drosophila* it leads to memory & learning defects. As the tau forms neurotoxic inclusion that are seen in Alzheimer's & Parkinson's disease. (51). Both under & over expression of LRRK2 can lead to loss of tyrosine hydroxylase (TH)-immunoreactive neurons. (51). If both the α -Syn and Tau are expressed simultaneously in *Drosophila* can harm the function of cytoskeleton which leads to neurodegeneration (52).

Amyotrophic lateral sclerosis (ALS) & frontotemporal dementia:

In this disease basically motor neurons are degenerated there are seven genes which is responsible for this which are studied in *Drosophila*. These are VAPB, VCP, C9ORF72, FUS, TDP-43, SOD-1, UBQLN-2. In the gene C9ORF72 which contain intronic hexanucleotide repeat (G4C2)_n get repeatedly expanded which is most common factor affecting ALS (53)(54). The aggregates commonly contain both ubiquitin and TDP-43, thereby uniting multiple ALS genes in a common. TDP-43 encodes the transactive response (TAR) DNA-binding protein, which can bind to both DNA and RNA. There is possibility that TDP53 incorporates the cryptic exons in the mRNA which make abrupt proteins which disrupts process of degradation leading to aggregates which are neurotoxic.

Huntington's disease:

This is caused due to generation of trinucleotide repeats which forms polyglutamine segment of 36 or more units in the Huntingtin (Htt) protein (55)(56). Despite of studying entire polyQ protein scientist focus on large poly Q domains. Some studies in *Drosophila* utilized fragments containing 12 exons & in some models only first three exons were used (59) (61). When the HDAC receptors are inhibited it declines the toxicity induced by polyglutamine. Also, the factors like photoreceptor quantification, motor performance, survival, circadian rhythm are studied for deficiency mutation & treatment strategy. (58) (59).

Ataxia Telangiectasia:

If the ataxia telangiectasia gene is mutated, in human it can cause problem in motor movements, increased infection frequency, increased cancer possibility & neurodegeneration (62). An atypical protein kinase is expressed as gene product of ATM. In *Drosophila* the homolog of ATM are telomerase fusion (tefu) & dATM. When telomerase function and dATM functions are studied, lot of information is obtained which elucidated the mechanism of ataxia telangiectasia. If the kinase activity is lost then it activates the innate immune response (63).

Aggression:

The term Aggression came from Latin word 'aggressio' means to attack. Aggression means the feeling of anger, vicious behaviour, or ready to attack someone. In physiology and social and behavioural sciences, the term aggression refers to the type of behaviour intending to cause physical or mental harm. Anger is a feeling and aggression is behaviour. The whole animal kingdom has militant behaviour which is necessary for their survival and reproduction. Aggressive gestures are used to acquire territory, food, or mates and in defense of the individual or its progeny against predators or conspecific rivals. Additionally, in some species, these behaviours are necessary to establish a social hierarchy. Several factors such as neurotransmitters, hormones, pheromones, sex, and individual anatomical differences have been studied in a variety of species that have an impact on aggression (64).

Drosophila melanogaster shows aggressive behaviour by some modules (behavioural patterns) which are: approaching - where one fly lowers his body and moves in the direction of the other; wing threats - where one fly speedily raises his wings toward its opponent; lunging - where one fly push himself on his opponent; boxing - where both flies raise on their hind legs and hit each other with their forelegs; tussling - where both flies tumble over each other; fencing or kicking; chasing and holding (64).

Several experiments have been performed to study the fighting behaviour in male and female *Drosophila melanogaster* independently, they were induced to fight. About behavioural patterns, it was observed that male and female *Drosophila melanogaster* share five common behavioural patterns that are high posture fencing, low posture fencing, lunge, walking retreat, approach. Whereas several gender selective patterns are seen – in females thrust with a wing threat, high posture fencing with wing threat, wing threat, head butt. In male's wing threat, hold, chase, running or flying retreat, wing flicking, boxing, and tussling (65), (66)

Most studies of learning and memory in *Drosophila* show that fights have used controlled classical or operant conditioning paradigms in which flies try a behavioural strategy and if it works they use that strategy frequently during subsequent meetings. In a variety of classical or operant conditioning paradigms, fruit flies generate learned behavioural responses that they associate with visual, tactile, or olfactory signals. Learning and memory are illustrated by the experiment performed in 2006, in the form of fight strategy adaptation by winners and losers and status-dependent behavioural changes; accompany aggression between pairs of socially naive male fruit flies. The study emphasises whether flies adopt distinct winning and losing strategies as hierarchical relationships are established, it showed that as soon as hierarchical relationships were established, behavioural strategies changed: lunging is the preferred strategy of winners and retreating of losers. Winners gradually lunged more and retreated less, whereas losers gradually lunged less and retreated more. At this point, behavioural changes last up to 30 min in the absence of an adversary. The time period examined here, which places them in the range of short- or mid-term memory. Whether flies remembered previous fights, do their fighting strategies change in subsequent fights; the result showed that flies were re-paired with familiar or unfamiliar adversaries, after 30 min of separation. In familiar pairings, fewer encounters were observed during the first 10 min of fighting than in unfamiliar pairings, and former losers fought differently against familiar winners than unfamiliar winners. Winner/winner, loser/loser, and naive/naive are paired which revealed that losers used low-intensity strategies in later fights and were unlikely to form new hierarchical relationships, compared with winners or socially naive flies. These results firmly support the idea that learning and memory accompany the

changes in social status resulting from fights between pairs of male fruit flies. An unusual aggression behaviour different from other animals is seen in *Drosophila* that is losing flies continually reengage winners. This tendency may be because flies have no dangerous weapons that threaten the health of a returning loser (67).

Environmental Factors:

The environmental sensitivity of insect brain development varies depending on specific brain regions and the type of environmental input or stress. Brain development and behaviour are sensitive to a variety of environmental influences including social interactions and physicochemical stressors. Multiple environmental factors interact to affect brain anatomical structures, circuits and cognitive function. Environmental factors also play important roles in sculpting and refining neural circuitry and consequent behaviour. Alternatively, disruption of central nervous system (CNS) development by environmental stress exposure (nutritive, chemical, electromagnetic and thermal) has been shown in every model system studied to date, including humans. Environmentally induced neuronal and behavioural plasticity is not limited to vertebrates, as both social and physicochemical cues affect insect brain development and function (70). Learning is defined as an adaptive response to change in environment, which results in the formation of memory due to molecular changes in neurons. Mushroom Bodies (MB) in *D. melanogaster* are the primary location for memory formation, including associative learning (68). According to research, adult *D. melanogaster* in response to heat stress, the mushroom bodies were the most volumetrically impaired among all of the brain structures. The effect is highly correlated with reduced odor-learning performance. Experimental studies revealed that ecologically relevant thermal stress affects development of MB in *Drosophila*. Daily hyperthermic episode throughout larval & pupal development highly disrupts MB anatomy by reducing intrinsic Kenyon cells (KC) neuron numbers. It also greatly impairs associative odour-learning in adults. Therefore, the duration & intensity of heat stress can impair brain development and learning potential (69).

Long Term Memory (LTM) is stored as functional modifications of relevant neural circuits in brain. The process known as Memory Consolidation requires learning-dependent transcriptional activation and de novo protein synthesis. But, till date it is not well understood that how this consolidated memory is maintained for longer period in brain, despite constant turnover of molecular substrates. Researchers demonstrate that environmental light play an important role in LTM maintenance. LTM is impaired when flies are kept in constant darkness (DD) during memory maintenance phase. Light activates brain neurons expressing neuropeptide pigment-dispersing factor (Pdf). Temporal activation of Pdf neurons compensated for DD-dependent LTM impairment and temporal knockdown of Pdf during memory maintenance phase impaired LTM in light/dark cycles. The transcription factor cAMP response element-binding protein (CREB) is required in memory center i.e. MBs for LTM maintenance and Pdf signalling regulates light-dependent transcription via CREB protein. Temporary memory can be consolidated into LTM through de novo protein synthesis and functional modifications of neuronal circuits in brain. And then, LTM requires continual maintenance to keep it for longer period against molecular turnover and cellular reorganization which may disrupt memory traces. However, mechanistically it is not well understood yet, but environmental light affects LTM by activating the CREB via peptidergic signalling (70). Another research demonstrates that when kept in dark, *Drosophila* loses the Long Term Memory of a traumatic event. As LTMs are very difficult to erase, this discovery may result in a crucial role to treat the patients suffering from trauma (Post-traumatic stress disorder). It may be beneficial in erasing life-altering traumatic Memories. But the mechanism of this process is still not understood and it opens up for the new discoveries in this area for future researchers (72).

Recent researches and findings revealed that memory retention is disrupted by copper (Cu²⁺) exposure in both young and adult flies. Old flies show more memory and learning impairments as compared to young flies. As copper is one of the essential element to all living organisms, but the repeated use of metal-enriched chemicals, fertilizers and organic substances may cause contamination at large scale. Altered levels of Cu²⁺ results in harmful effects and can be associated with memory and cognitive dysfunction.

Exposure of *Drosophila* eggs to Cu²⁺ increased mortality of larvae, pupae and adults and decreased memory retention in adults. Also, it is demonstrated that male flies were more susceptible to Cu²⁺ toxicity than females (71). As this research is very recent, more investigation is needed in upcoming future to confirm the facts and findings entirely. More precise knowledge in this area of research is awaited.

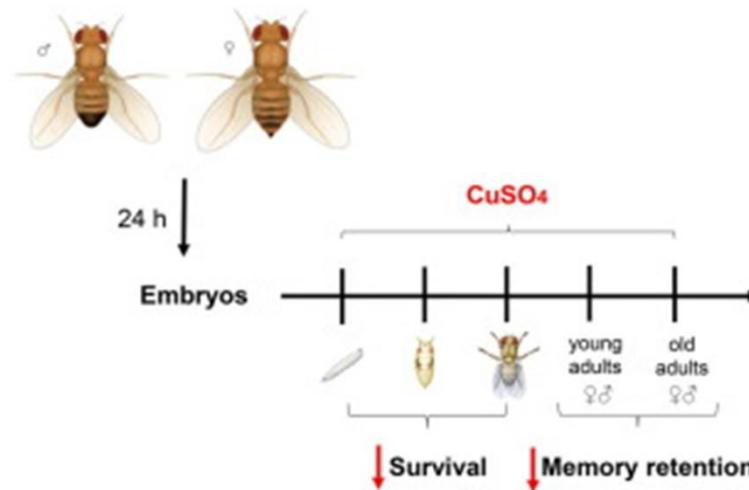


Fig: copper (cu²⁺) Exposure

III. CONCLUSION

Drosophila has been proposed as a model organism in biological research since very long time because of its short life cycle, genetic similarity to mammals and also it is easy to culture. Abundance of work had done on *Drosophila melanogaster* to study memory and learning. In addition many factors like sleep, sleep deprivation, circadian rhythm, ageing, alcoholism, aggressiveness, starvation, environmental factors, oxidative stress have an impact on learning and memory either positively or negatively. All the above mentioned factors are in relation to memory and they are inter connected with each other effect of this factors give rise to many neurobiological disorder which can be studied in *Drosophila* as it has genetically similar neural circuit and functioning.

In this article we have tried to congregate all the factors affecting and influencing memory to study the memory in deep. This article assembled discrete research on memory in one single paper which will be helpful for upcoming researches and scholar.

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