IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Beyond Reward: Dynamic Roles Of Octopaminergic Signaling In Associative Learning And Behavioral Plasticity

Denzil Oscar Singh[1] and **Vivek Kumar Dixit**[2]

[1] **M.Sc., Department of Zoology, BSNV PG College, Lucknow, India**

[2] **Assistant Professor, Department of Zoology, BSNV PG College, Lucknow, India**

Corresponding author:

Denzil Oscar Singh

Abstract:-

Animals dwell on associative learning to adaptively modify their behavior with respect to their environmental experiences and internal physiological needs. Historically, among invertebrates, **octopamine** has been regarded as the principle neuromodulator responsible for appetitive reinforcement or learning. Opposing to which are dopaminergic neural pathways which associates with aversive learning. Earlier classical studies over insect conditioning established a dichotomous framework where octopamine mediated reward-related memory formation, whereas **dopamine** encodes for punishment signals. It was when molecular, circuit-level and behavioral evidences were investigated, octopaminergic signaling was observed to be modulating more dynamically and context-dependently, which are further unexpected from octopaminergic pathways previously.

The recent studies and findings demonstrates octopamine to be interacting with over distributed reinforcement networks involving mushroom body circuitry, receptor-specific intracellular signaling, and dopaminergic neurons, rather than simply functioning as an isolated reward transmitter. The receptors family through which octopamine modulates and contributes towards appetitive learning includes- OAMB and Octβ. Through these receptors octopamine regulates appetitive processing, motivational regulation, and adaptive behavioral prioritization depending on neural substrate and physiological states. Specifically, layered reinforcement signaling between octopamine and dopamine reveals that these their is a substantial functional integration among these two neural pathways, rather than strict neurochemical segregation. Furthermore, metabolic as well as endocrine factors which includes- starvation state, glycogen availability, and insulin-like signaling critically moulds octopamine-dependent memory formation and reinforcement allocation processes.

The present review synthesizes classical and emerging perspectives over octopaminergic function in associative learning and behavioral plasticity across invertebrate systems, special emphasis was given to **Drosophila melanogaster** as the model organism. We discuss the evolution of reinforcement theories from simple appetitive-valence models and moves towards distributed neuromodulatory frameworks where octopamine acts as a flexible integrator of sensory valence, internal state, and circuit-level plasticity. Finally, we highlights the evolutionary parallels between octopaminergic and adrenergic signaling systems and proposes future directions for understanding how neuromodulatory architectures coordinates for adaptive behavior across species.

Keywords- Octopamine, Associative learning, Behavioral plasticity, Mushroom body, Neuromodulation, Dopamine, Appetitive conditioning, Reinforcement signaling, Invertebrate neuroscience, Drosophila melanogaster.

Introduction:-

Organisms depends over associative learning as a fundamental form of behavioral plasticity, through which they modify future responses based on their previously gained experiences. Associative learning enables organisms to optimize survival-related behaviors like- foraging, predator avoidance, reproduction, and social interaction. This is achieved via linking environmental cues with rewarding or punishing outcomes. Across both vertebrates and invertebrates, these adaptive processes are critically shaped by the action of neuromodulators, which regulates reinforcement, motivation, attention, and memory formation. Biogenic amines have emerged as central regulators of behavioral flexibility and neural plasticity among these neuromodulators.

Among invertebrate, including insects, octopamine has long been considered as a principal mediator of appetitive reinforcement and motivational signaling (**Schwaerzel et al.,2003; Giurfa,2006**). In several aspects, it is analogous to mammalian adrenergic systems. Octopamine influences a wide range of physiological and behavioral processes including- arousal, locomotion, feeding, aggression, sensory responsiveness, and learning. Earlier olfactory conditioning paradigmatic studies, particularly in Drosophila melanogaster and honeybees, established a classical framework where octopamine mediated appetitive learning and dopamine encoded aversive reinforcement (**Schwaerzel et al.,2003)**. This dichotomous model substantially shaped the conceptual understanding of insect reinforcement systems for nearly two decades.

This framework was supported by initial experimental evidences, which demonstrated that the disruption of octopaminergic signaling impairs appetitive olfactory conditioning while no significant effect being observed over aversive memory formation. Conversely, dopaminergic manipulations selectively disrupted punishment-associated learning. These findings indicates that distinct neuromodulators encodes for opposing motivational valences through convergent mushroom body circuitry. Subsequent studies additionally demonstrates that octopamine acts as an instructive reinforcement signal (**Giurfa,2006**), that assigns motivational significance to conditioned stimuli rather than merely altering generalized arousal or behavioral excitability. Such observations positioned octopamine as a dedicated “reward neurotransmitter ”found within insect learning systems.

However, recent advancement in molecular genetics, functional imaging, receptor biology, and neural circuit analysis have considerably expanded this classical interpretation. Newly emerging evidences indicates that

octopaminergic signaling operates via receptor-specific, circuit-dependent, and physiologically regulated mechanisms that extends beyond simple appetitive reinforcements. Studies that employs temporally controlled neural activation and receptor-specific manipulations have demonstrated that octopaminergic signaling dependent memory formation frequently requires interactions with dopaminergic neurons (**Burke et al.,2012**) along with mushroom body-targeted reinforcement circuits. In particular, signaling through OAMB receptors and Octβ receptor subtypes (**Kim et al.,2013; Sabandal et al,2020**) has revealed substantial functional specialization across distinct neural populations, including differential contributions to appetitive and aversive learning processes.

In parallel, growing evidences suggested that associative learning cannot be adequately explained through rigid neurochemical segregation of motivational valence. Instead, octopamine and dopamine appears to functions cooperatively (**Burke et al.,2012; Sabandal et al.,2020**) within distributed reinforcement networks that dynamically integrate sensory information, motivational state, and behavioral context. Octopaminergic signaling, for example, has been implicated in prediction-error processing (**Mizunami & Matsumoto,2017**), aversive reinforcement compensation during starvation, and state-dependent modulation of memory allocation. Internal metabolic signals like- glycogen availability and insulin-like signaling (**Berger et al.,2024**), further demonstrated to influence octopamine-dependent reinforcement strength and memory persistence, thus indicates that physiological state critically shapes or moulds learning-related neural plasticity.

Additionally, other than behavioral regulation, comparative neuroanatomical studies have highlighted striking parallels between octopaminergic organization in insects and adrenergic modulation in vertebrates olfactory systems (**Sinakevitch et al.,2018**). Despite substantial evolutionary divergences, the principles of neuromodulatory architectures, glomerular processing, and reinforcement integration have been conserved. This suggests that insect models may provide broader insights into the evolution of adaptive learning systems. Evolutionary diversification of octopamine receptor families (**Yang et. al.,2026**) additionally indicates that aminergic signaling pathways remain highly flexible and subject to lineage-specific selective pressures, which potentially contributes to species-specific behavioral adaptation (Figure 1).

In this review, we synthesized classical and contemporary perspectives on octopaminergic function in associative learning and behavioral plasticity. With the primary focus over insect models, we examine the molecular architecture of octopaminergic signaling, their role in mushroom body reinforcement circuits, interactions with dopaminergic pathways, and its interactions with dopaminergic pathways, along with its integration with metabolic and motivational states. We further discusses how recent findings challenges traditional reward-centric interpretation and support a broader framework where octopamine functions as as dynamic neuromodulators which integrates and coordinates adaptive behavioral responses across changing environmental and physiological contexts.

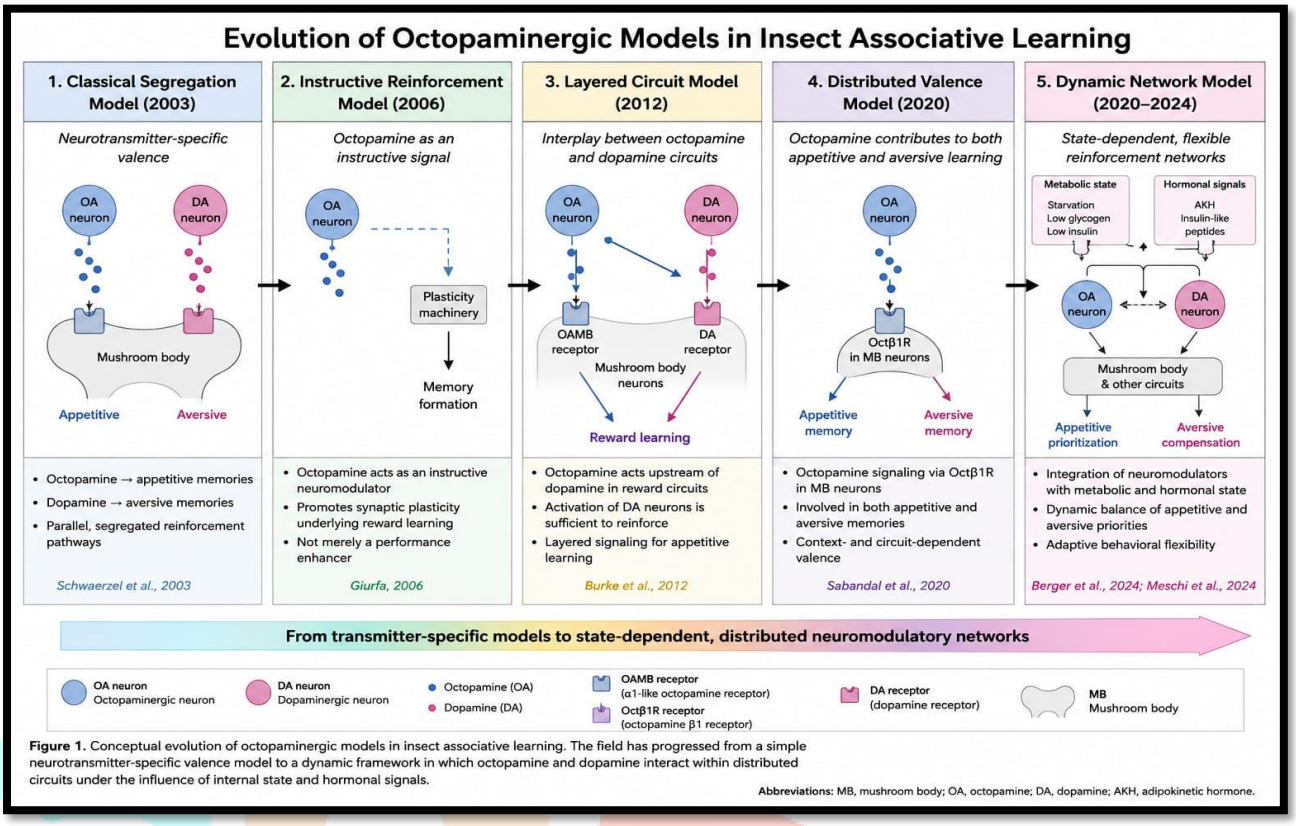

Figure 1. Conceptual evolution of octopaminergic models in insect associative learning. The field has progressed from a simple neurotransmitter-specific valence model to a dynamic framework in which octopamine and dopamine interact within distributed circuits under the influence of internal state and hormonal signals.

Abbreviations: MB, mushroom body; OA, octopamine; DA, dopamine; AKH, adipokinetic hormone.

Figure 1. Evolution of conceptual models of octopaminergic signaling in associative learning.

Early models proposed strict neurochemical segregation in which octopamine mediated appetitive reinforcement while dopamine encoded aversive learning. Subsequent studies introduced instructive reinforcement functions and layered octopaminergic-dopaminergic circuit interactions within mushroom body pathways. More recent evidence supports a distributed and context-dependent reinforcement framework in which octopaminergic signaling integrates receptor-specific modulation, internal metabolic state, endocrine signaling, and cooperative neuromodulatory network interactions to regulate associative learning and behavioral plasticity.

Abbreviations:

OA, octopamine; DA, dopamine; MB, mushroom body; OAMB, octopamine receptor in mushroom body neurons.

Octopaminergic Signaling Architecture in Invertebrates:-

Biogenic amines constitute an evolutionarily conserved class of neuromodulators. These neuromodulators regulates diverse physiological and behavioral functions across animal taxa. Among invertebrates, octopamine is one of the principal aminergic signaling molecules and has been extensively implicated in the modulation of arousal, locomotion, feeding behavior, aggression, sensory responsiveness, and associative learning. Octopamine is often functionally described as analogous to vertebrate nonadrenergic system (**Sinakevitch et al.,2018**). It's actions in insect nervous systems yet, exhibit substantial receptor diversity, circuit specificity, and context-dependent functional complexity.

Octopamine is synthesized from tyramine via the catalytic activity of tyramine β-hydroxylase and is widely distributed throughout the central and peripheral nervous systems of insects. Octopaminergic neurons innervates multiple brain regions that are associated with sensory integration, motor coordination, reinforcement processing, and memory formation, including the antennal lobes and mushroom bodies.

Octopamine influences both early sensory processing and higher-order associative circuitry via these projections. Further analyses of comparative neuroanatomy of octopaminergic and tyraminergic fibers within insect olfactory neurophils displayed organizational similarities with nonadrenergic projections in vertebrates olfactory structures, this supports the existence of conserved principles of neuromodulatory regulation across phyla.

Octopaminergic signaling functional diversity is mediated through multiple receptor subclasses, that exhibits distinct intracellular signaling and neural distributions. In Drosophila melanogaster, at least six octopamine receptor types have been identified (**Yang et al.,2026**), including OAMB, Oct-alpha2R, Octβ1R, Octβ2R, Octβ3R, and Oct-TyrR. These receptors belongs to the G-protein-coupled receptor (GPCR) superfamily and exhibit considerable molecular and functional heterogeneity. Receptor-specific signaling enables octopamine to regulate diverse forms of neural plasticity and behavioral output through distinct intracellular pathways involving calcium mobilizing, cyclic AMP (cAMP) signaling, and modulation of neuronal excitability.

Among these receptors, OAMB has emerged as a critical mediator of appetitive associative learning (**Kim et al.,2013**). OAMB receptors are prominently expressed within mushroom bodies alphaβ and gamma neurons, where they contribute to olfactory reinforcement processing. Functional studies have demonstrated that loss of OAMB signaling severely impairs appetitive conditioning, establishing a direct casual role for octopaminergic receptor activation in memory formation. Importantly, OAMB activation induces intracellular calcium elevation (**Kim et al.,2013**) and, depending on receptor isoform, can additionally stimulate cAMP production, indicating that octopamine-dependent reinforcement involves coordinated second-messenger signaling rather than simple excitatory transmission.

Additionally to OAMB-mediated pathways, β-adrenergic-like receptors including Octβ1R and Octβ2R contribute substantially to reinforcement signaling and behavioral modulation. Recent evidences suggests that Octβ1R signaling participates in both appetitive and aversive learning (**Sabandal et al.,2020**) depending on receptor localization within distinct neural circuits. For example, Octβ1R activity in projection neurons has been associated with appetitive olfactory conditioning. On the other hand signaling within mushroom body alphaβ neurons contributes for aversive learning processes. These findings demonstrates that behavioral valence cannot be inferred solely from neurotransmitter identity, but instead emerges through receptor-specific and circuit-dependent neuromodulatory interactions.

Octopaminergic signaling also exhibits substantial functional integration with dopaminergic reinforcement pathways. Studies employing temporally controlled neural activation have shown that octopamine-dependent appetitive memory formation frequently requires downstream activation of mushroom-body-targeted dopaminergic neurons (**Burke et al.,2012**). In these circuits, octopamine acts through OAMB receptors to induce intracellular calcium signaling in dopaminergic neurons, which subsequently drive reinforcement-associated plasticity within mushroom body networks. Such layered signaling architectures indicates that octopamine functions as a part of a distributed neuromodulatory system coordinating multiple stages of associative memory formation, rather than functioning as an isolated reinforcement signal.

Recent evolutionary analyses further suggests that octopamine receptor system remains highly adaptable and subject to lineage-specific selective pressures. Positive selection observed in Octβ receptor subtypes (**Yang et al.,2026**), particularly within ligand-binding and signal-transduction domains, highlights the evolutionary flexibility of aminergic signaling architectures in insects. This diversification may contribute to species-specific modulation of reinforcement processing, motivational state, and behavioral specialization. Consequently, octopaminergic systems should not be viewed as static or uniformity conserved pathways, but

rather as dynamically evolving neuromodulatory networks capable of supporting diverse ecological and behavioral adaptation.

Collectively, current evidence supports a model in which octopaminergic signaling operates through receptor-specific, circuit-dependent, and evolutionary flexible mechanisms that extend far beyond generalized reward transmission. The molecular complexity of octopamine receptors and their integration within reinforcement circuitry provide the mechanistic foundation through which octopamine dynamically regulates associative learning and behavioral plasticity in invertebrate nervous systems.

Classical Roles of Octopamine in Appetitive Associative Learning:-

Earliest experimental investigations of octopaminergic function in insect learning established octopamine as a principal mediator of appetitive reinforcement. Associative learning paradigms demonstrates that animals assigns motivational significance to previously neutral sensory cues. This is achieved through repeated pairing with rewarding or aversive stimuli. Initial studies performed over Drosophila melanogaster, crickets and honeybees demonstrated that disruption of octopaminergic signaling selectively impaired reward-associated memory formation while leaving aversive conditioning relatively intact. These observations lead to the emergence of the classical reinforcement dichotomy (**Schwaerzel et al.,2003**) in which octopamine encoded appetitive valence and dopamine mediated punishment-related learning.

This framework is supported by one of the foundational studies, which demonstrated that dopamine and octopamine differentiates among aversive and appetitive olfactory memories (**Schwaerzel et al.,2003**) via distinct modulatory pathways that are convergent on shared mushroom body circuitry. Importantly, cyclic AMP signaling within the same subset of mushroom body intrinsic neurons was shown to be both necessary and sufficient for the formation of different associative memories depending on motivational context. These findings suggested that reinforcement specificity was determined by neuromodulatory inputs that assigns distinct motivational values to sensory representations, rather than by anatomically isolated memory systems. Consequently, octopamine became widely regarded as the primary appetitive reinforcement signal in insects brains.

Further conceptual works refined this interpretation by proposing octopamine to functions as an instructive neuromodulator (**Giurfa,2006**) during associative learning. Rather than globally increasing arousal or enhancing behavioral activity non-specifically, octopamine was suggested to assign motivational valence to conditioned stimuli and guide reinforcement-dependent plasticity. In this framework, octopaminergic signaling allows insects to categorize environmental cues as per their predicted biological significance, thereby shaping future behavioral responses toward beneficial outcomes such as nutrient acquisition. This perspective positioned octopamine as an active determinant of reinforcement coding rather than a passive modulator of neural excitability.

Experimental evidences from Pavlovian olfactory conditioning paradigms strongly supported this reward-associated role. Octopaminergic signaling was found to be essential for appetitive learning in larval and adult insects (**Burke et al.,2012**). Appetitive learning was induced by sucrose reward and other nutrient-associated stimuli. Genetic disruption of octopaminergic neurons or receptor pathways consistently impairs appetitive conditioned responses, this demonstrates that octopamine contributes directly to reinforcement-dependent memory formation. Furthermore, activation of octopaminergic neurons substituted for natural reward stimuli

under certain experimental conditions. This indicates that octopamine conveys biological meaningful reinforced information within associative learning circuits.

Researches over crickets further extended these observations by demonstrating that during appetitive learning, octopaminergic neurons encodes prediction-error-like signals (**Mizunami & Matsumoto,2017**). In these model insects , octopamine-mediated reinforcement depends on discrepancies between expected and actual rewarding outcomes. This demonstrates functional parallels with reinforcement-learning mechanisms observed in vertebrates. Such significant findings explains the conceptual understanding of octopamine from being a simple "reward chemical" towards a more computationally sophisticated reinforcement signal that is involved in evaluating behavioral outcomes and updating associative memories.

Although the classical appetitive reinforcement model was supported by strong experimental evidences, yet several observations gradually revealed limitations within this framework. Octopamine was initially considered to be functionally segregated from dopaminergic aversive pathways. But recently emerging evidences indicates substantial overlapping and interactions between these systems. Furthermore, the same sensory stimulus could generate distinct associative memories depending on the internal state, environmental context, and neural circuit configuration. These findings suggests that reinforcement processing in insect brains could not be fully explained through rigid neurochemical segregations alone.

Nevertheless, the classical model provided an essential conceptual foundation for understanding insect associative learning and establishes the importance of biogenic amines in reinforcement processing. By linking octopamine to motivational valence assignment and appetitive conditioning, early studies paved the way for later investigations into receptor-specific signaling, mushroom body circuitry, and distributed neuromodulatory interactions. Importantly, these foundational discoveries continued to inform contemporary efforts to reinterpret octopaminergic signaling within broader frameworks of behavioral flexibility and adaptive neural plasticity.

Mushroom Body Circuits and Reinforcement Integration:-

Mushroom body represents one of the principal higher-order associative centres in the insect brain. It plays a central role in sensory integration, reinforcement processing, and memory formation. In olfactory conditioning paradigms, sensory information were observed to be transmitted from the antennal lobe projection neurons, that converges onto mushroom body intrinsic neurons. Here conditioned stimuli are integrated with neuromodulatory reinforcement signals. Early reinforcement models put forwarded that appetitive and aversive memories were encoded through relatively independent octopaminergic and dopaminergic pathways. Even then, accumulating molecular and circuit-level evidences and findings suggests that associative learning emerges through layered and highly interconnected neuromodulatory architectures.

One of the major discovery that shifted the conceptual idea regarding octopamine-dependent appetitive memory formation was that this process requires the functional interactions with dopaminergic reinforcement circuits (**Burke et al.,2012**). Via the studies using temporal controlled neural manipulations in Drosophila melanogaster, it was concluded that octopaminergic signaling alone is not sufficient to establish appetitive memory formation. Instead, octopamine acts upstream of specific mushroom-body targeted dopaminergic neurons, they then subsequently mediates reinforcement-dependent plasticity within its associated structures

and circuits. These findings fundamentally questions the classical view and challenging the strictly segregated reinforcement system view. Additionally it introduces the concept of layered reward signaling (**Burke et al.,2012**).

When viewing mechanistically, octopaminergic neurons was observed to be responding to rewarding stimuli like- sucrose and activated dopamine neurons via receptor-mediated intracellular signalling pathways. Centrally in this process, alpha1-adrenergic-like receptor OAMB is involved. It is expressed within the sunsets of mushroom-body associated dopaminergic neurons and mushroom body intrinsic neurons (**Kim et al.,2013**). Over getting activated, OAMB induces levels of intracellular calcium to increase (**Kim et al.,2013**) along with modulating downstream signaling cascades that are associated with synaptic plasticity and encodes reinforcement. Experimentally activating these dopaminergic neurons substitutes for natural reward stimuli (**Burke et al.,2012**) leading to appetitive memory formation, even in animals that lacks functional octopaminergic signaling. This indicates that dopaminergic reinforcement circuits operates as critical downstream effector of octopamine-dependent reward processing.

Notably, OAMB signaling is not only restricted within a single intracellular mechanism. Varied receptor isoforms collectively contributes to calcium mobilization and to cyclic AMP (cAMP) productions. This process enables complex modulations of neuronal excitability and synaptic plasticity. These signaling pathways present within mushroom body alpha, beta and gamma integrates together and provides a mechanistic basis for reinforcement-dependent memory encoding. When these OAMB receptors gets impaired or disrupted functionally, causes severe impairment in appetitive olfactory conditioning. Due to this receptor-specificity octopaminergic signaling acts as an essential component of associative learning circuitry.

Other than OAMB-mediated pathways, β-adrenergic-like receptors of octopamine additionally contributes to reinforcement integration across distinct neural populations. The Octβ receptors takes part in both appetitive and aversive conditioning with context of neural localization and circuitry. For example, Octβ1R signaling within projection neurons (**Sabandal et al.,2020**) contributes for appetitive reinforcement. On the other hand signaling within mushroom body alpha β neurons influences aversive learning. From these observations it has been demonstrated that reinforcement valence is not determined by neurotransmitter identity solely but instead it emerges through circuit-specific receptor activation and distributed network interactions.

Therefore, the mushroom body does not functions as a passive memory storage structure, rather it functions as a dynamic reinforcement integration hub, where multiple neuromodulatory systems together shapes behavioral outcomes. Within this framework, octopamine coordinates the process of sensory reinforcement by interacting with dopaminergic pathway, intracellular signaling cascades, and context-dependent circuit modulation. This organization allows associative memories to be flexibly regulated rather than being rigid, as per the motivational significance, environmental conditions, and physiological demands of the insect.

The evident view of mushroom body reinforcement circuitry strongly questions the earlier established neurochemical dichotomies, according to which fixed behavioral functions were assigned to individual neuromodulators. Instead of acting as isolated “reward” or “punishment” transmitters, both octopamine and dopamine seems to join forces within the distributed reinforcement architecture. These structures collectively regulates associative plasticity. This changes the view from transmitter-centered models towards the circuit-

level integrations. This therefore represents one of the most significant conceptual advances among insect learning neuroscience.

Additional, the layered organization of octopaminergic and dopaminergic signaling shares notable conceptual parallels among insect and vertebrates reinforcement systems. In vertebrate systems neuromodulators coordinate prediction-error processing, motivation salience, and adaptive behavioral selection. All this is coordinated via interconnected neural networks. Therefore, insects mushroom body circuitry provides a valuable model for investigating general principles of neuromodulatory reinforcement interactions across species.

Cooperative Neuromodulation and distributed valence processing:-

According to the traditional interpretations, insect reinforcement systems relied mainly on a neurochemical dichotomy, where octopamine mediated appetitive learning while dopamine encoded aversive reinforcement. Where on one hand this framework provided an important foundation making us understand associative conditioning. Conversely, recent evidences increasingly demonstrates that motivational valence cannot be rigidly assigned to individual neuromodulators. Instead, associative learning appears to emerge through cooperative interactions among distributed neuromodulatory pathways whose functional outcomes depend on receptor identity, neural substrate, physiological state, and behavioral context.

This classical segregation model was strongly challenged by the studies which demonstrated that octopamine contributes not only for appetitive conditioning but it also accords for aversive learning (**Sabandal et al.,2020**) under specific circuit configurations. Over analysing specific receptors, β-adrenergic-like octopamine receptors were found to be participating in both forms of associative conditioning depending on their localization within the olfactory and mushroom body circuits. For example, Octβ1R signaling contributes in appetitive olfactory learning in projection neurons (**Sabandal et al.,2020**), whereas signaling within mushroom bodies alpha β neurons influences aversive memory formation. These findings indicates that behavioral valence is not intrinsically encoded by neurotransmitter class but instead it emerges through circuit-dependent modulation of reinforcement pathways.

Notably, cooperative signaling between octopaminergic and dopaminergic systems seems essential for multiple types of associative plasticity. From the experimental evidences it has been demonstrated that octopamine-Octβ1R and dopamine-dAD1 signaling collectively modulates appetitive and aversive learning processes. In contrast to this, octopamine-OAMB pathways facilitates appetitive reinforcement selectively. From these interactions it has been demonstrated that reinforcement coding is distributed through interconnected neuromodulatory networks rather simply by isolated chemical channels. Through this framework octopamine and dopamine cooperatively shapes behavioral adaptation by coordinating the modulation of synaptic plasticity, motivational salience, and sensory valuation.

Through this distributed architecture provides significant functional advantages in adaptive behavior. Environmental stimuli rarely possess fixed biological meaning, and the same sensory cue may predicts-reward, threat or neutrality which will be dependent based on the ecological conditions and internal physiological demands of the insect. Due to flexible neuromodulatory integrations, associative circuits dynamically reassigns motivational significance as per the changing contexts. Octopamine interacts across

multiple receptors systems and neural populations, through thus it can contribute to reinforcement flexibility without getting restricted to a singular behavioral role alone.

Further on, the prediction-error processing (**Mizunami & Matsumoto, 2017**) illustrates to the complexities of the distributed reinforcement coding. The cricket conditioning paradigms reveals octopaminergic neurons to be involved in discrepancy signaling between expected and actual rewarding outcomes. This suggests that octopamine participates in evaluative computations rather than simply transmitting reward alone. These mechanisms acts similarly as reinforcement-learning frameworks of vertebrates neuroscience, where adaptive behaviors depends on continuously updating predictive associations basis of experiences. This involvement of octopamine in prediction-error like signaling hence supports the broader interpretation of octopaminergic systems as dynamic regulators of behavioral adaptation.

Evidences for distributed valence processing, additionally emerges from studies over interactions between appetitive and aversive memory systems. Among honey bees study model, dopaminergic signaling has been observed to interfere with appetitive long-term memory formation (**Klappenbach et al.,2013**), and it also additionally blocks dopamine receptors to enhance appetitive consolidation. Collectively, these observations demonstrates that reward and punishment related pathways interacts with each other competitively and cooperatively during memory allocations. This prevents maladaptive overrepresentation of a single motivational state. Therefore, associative learning seems to include continuous balancing from competing reinforcement systems, rather than simply encoding positive and negative valence independently.

The growing recognition of cooperative neuromodulation substantially alters the conceptual understanding of insect learning systems. Instead of assigning discrete behavioral functions to individual neurotransmitters, contemporary models empathizes that distributive network interactions may integrate sensory input, motivational significance, environment context, along with internal physiological conditions. Octopamine functions as a flexible modulatory component within these architectures, it's behavior effects emerges through receptor-specific interactions with broader reinforcement circuitry.

Collectively, these insights supports a transition away from reductionist transmitter-centred frameworks towards integrated system-level models of associative learning. Such model profoundly accounts for the remarkable behavioral flexibility, observed in insects. It also provides a more accurate representation of how neuromodulatory networks dynamically coordinates adaptive responses in complex and altering environments.

Metabolic State, Motivation, and Memory Regulation:-

For associative learning to occur it needs to be connected with physiological state of the insect. As animals continuously adjusts reinforcements processing, motivational priorities, and memory allocation according to their internal metabolic demands and environmental resource availability. Contemporary studies demonstrates that octopamine is centrally involved in integrating these physiological signals, knitting the associative learning circuitry. This therefore links behavioral plasticity to energy homeostasis and adaptive survival strategies. These rulings substantially elaborates the classical interpretation of octopamine from a dedicated appetitive reinforcement signal towards a broader regulator of state-dependent behavioral modulation.

Among the most significant advancement with respect to this statement has been experimentally recorder in Drosophila melanogaster. In these flies it has been demonstrated that starvation state dynamically influences the type and persistence of food-associated memory formation processes. Experimental evidences reveals that the duration of starvation eventually determines (**Berger et al.,2024**) whether the flies will preferentially form short-term appetitive memory or longer-lasting intermediate memory states. Additionally, the internal glycogen reserves present within muscles and adipose tissues, modulates the intensity with which sucrose-associated information will be encoded. These holdings reveal that reinforcement strength is not fixed rather it depends on the interactions between external and reward stimuli along with the internal energetic conditions.

Mechanistically, insulin-like signaling within the octopaminergic reward neurons (**Berger et al.,2024**) has emerged as a significant pathway that links metabolic state with reinforcement processing. Octopamine integrates information about the internal energy availability, as well as it subsequently regulates memory formation according to the insects physiological needs. With elevated levels of internally stored glycogen, the reinforcement value of sucrose is reduced. Conversely, prolonged starvation enhances the stability and motivational significance of appetitive-food-related memories. Such regulations likely serves adaptive functions by prioritizing nutrient acquisition during the periods of energetic deficit, alongside preventing excessive reinforcement of feeding behavior during satiety.

Importantly, octopamine memory formation modulation is not uniformly facilitatory. Recent evidences suggests that octopamine can suppress long-term memory formation (**Berger et al.,2024**) under the influence of certain metabolic conditions. This indicates that octopaminergic signaling participates in balancing memory persistence against energetic costs. This observation directly challenges the simplistic assumption according to which stronger octopaminergic activity necessarily produces enhanced reward memory. Instead, octopamine appears to regulate the allocation and duration of associative memories in a context-dependent manner that optimizes behavioral efficiency and resource utilization.

Additionally to appetitive conditioning and reinforcement, metabolic states have more broader influences. Hunger-induced modulation of aversive learning circuits further signals towards the flexibility of octopaminergic systems during adaptive behavioral prioritization. At the time of starvation, aversively reinforcing dopaminergic neurons are inhibited (**Meschi et al.,2024**). This facilitates the expression of food-seeking behaviors. However, excessive suppression of aversive processing could compromise survival as it impairs avoidance of harmful stimuli. To compensate for this drawback, endocrine adipokinetic hormone (AKH) signaling engages octopaminergic pathways (**Meschi et al.,2024**) that preserves aversive reinforcement at the time of metabolic stress.

Notably, specific octopaminergic neurons within the ascending ventral brain pathways are needed for maintaining shock and bitter taste reinforced learning during chronic hunger. These compensatory mechanisms allows hungry animals to continually respond appropriately to threatening or harmful environmental cues, along with simultaneous prioritization of food acquisition. Such findings highlights the remarkable flexibility of octopaminergic modulation and demonstrates that reinforcement systems are dynamically reconfigured as per the competing physiological and behavioral demands.

The integration of metabolic signaling with associative learning circuits strongly supports the emerging view that reinforcement processing operates via distributed and adaptive neuromodulatory networks. Instead of

encoding fixed motivational categories, octopaminergic pathways continuously evaluates physiological context and adjust behavioral priorities accordingly. Through their interactions with insulin signals, endocrine pathways, dopaminergic circuits and mushroom body reinforcement networks, octopamine coordinates the balance between memory formation, motivational state, and energetic necessity.

These observations substantially broadens the conceptual significance of octopaminergic signaling in insect neuroscience. Octopamine therefore, should be understood as a dynamic regulator of behavioral allocations that is capable of integrating sensory information with internal physiological state, rather than simply imaging it as a reward-associated neurotransmitter. This capacity of state-dependent modulation likely contributes significantly to the ecological adaptability and behavioral flexibility observed across diverse invertebrate species.

Evolutionary Perspective and Functional Conservation:-

Although octopamine is predominantly associated with invertebrate nervous systems, which is supported by accumulating comparative evidences which suggests that several organizational and functional principles of octopaminergic signaling exhibits notable parallels to that of vertebrates adrenergic neuromodulation. These similarities have increased the interest in insect reinforcement systems to be used as experimentally tractable models serving to investigating the conserved mechanisms which underlies sensory integrations, motivational regulations, and adaptive behavioral plasticity. Simultaneously, evolutionary diversification of octopaminergic pathways highlights the flexibility of aminergic signaling systems that shapes species-specific behavioral strategies.

Over comparing the studies of olfactory systems of insects to that of mammals it has been revealed that despite the substantial evolution of these structures are divergent but their structure are similar to each other (**Sinakevitch et al,.2018**). In both mammals and insects, sensory inputs from the olfactory receptor neurons are initially processed within the synaptically dense neuropils, that are organized into glomerular structures before being transmitted to higher-order associative centers. Within these glomeruli, it is the neuromodulatory fibers that regulates sensory gain, signal discrimination, and behavioral salience via the extensive centrifugal modulation. Among honeybees, octopaminergic and tyraminergic projections (**Sinakevitch et al.,2018**) display distribution patterns that are similar to noradrenergic fibers found within the mammalian olfactory bulbs. This suggests that there exists a convergent or evolutionarily conserved principles of modulatory organization among insects and mammals.

These parallels extends beyond anatomical organization regulating functional roles I reinforcement and motivational processing. In vertebrates, adrenergic systems regulates arousal, attention stress responses, memory consolidation, and adaptive behavioral prioritization. Similarly, in insects octopaminergic signaling modulates locomotory activity, feeding behavior, aggression, sensory responsiveness, reward processing, and associative learning. Although the direct evolutionary equivalence between octopamine and vertebrate catecholamines should be avoided, but then too the functional resemblance between octopaminergic and adrenergic systems supports the interpretation of octopamine to be similar as adrenergic-like neuromodulator that coordinates adaptive behavioral state transitions.

Importantly, the insects learning systems provide several experimental advantages for dissecting reinforcement circuitry. Comparing this with that of vertebrate brains, the insect nervous systems possess relatively compact and accessible neural architectures along with retaining the sophisticated forms of associative learning and behavioral flexibility. Thus combination permits a high-resolution investigation of

neuromodulatory interactions, receptors-specific signaling and circuit-level plasticity that would be considerably more difficult to resolve in larger vertebrate systems. Consequently, studies regarding octopaminergic signaling in insect models have contributed substantially to broader theoretical frameworks concerning reinforcement integration and motivational computation.

Evolutionary analysis of octopamine receptor families further emphasizes to the ability of aminergic signaling pathways. In Drosophila melanogaster, many octopamine receptor subtypes (**Yang e. al.,2026**) exhibits distinct molecular characteristics, intracellular signaling properties, and behavioral functions. Affirmation of positive selection within ligand-binding (**Yang et al.,2026**) and signal-transduction domains of certain Octβ receptor subtypes reveals that octopaminergic signaling systems remain evolutionarily flexible and responsive to lineage-specific ecological pressures. Such diversification may facilitate species-specific optimization of reinforcement sensitivity, motivational regulation, and behavioral specialization.

The evolutionary plasticity of octopamine receptors additionally supports a broader reinterpretation of neuromodulatory systems as a dynamic architecture, rather than being rigidly conserved signaling modules. Small modifications in the receptor distributions, ligand affinity, or intracellular coupling can potentially generates substantial changes in reinforcement processing and behavioral outputs. This flexibility may explains the reason of why octopaminergic systems contributes to diverse behavioral phenotypes across insect taxa while they still preserves their core organizational principles that are related to associated learning and motivational modulation.

Comparative perspectives additionally reinforces the growing recognition regarding that the behavioral valence cannot be reduced to singular neurotransmitter identities. Across species, adaptive behavior emerges through interactions between distributed neuromodulatory networks that integrates sensory information, physiological state, environmental uncertainty, and prior experiences. The apparent convergence between insect octopaminergic systems and vertebrate adrenergic reinforcement mechanisms therefore highlighting the possibility that the fundamental principles of neuromodulatory organization may transcend phylogenetic boundaries despite being substantially divergent molecularly.

Collectively, current evidences positions octopaminergic signaling as both an evolutionary informative and mechanistically versatile system for understanding associative learning and behavioral plasticity. Via combining the molecular specificity, the circuit level accessibility, and behavioral complexity, the insect octopaminergic networks provides valuable opportunities for investigating general principles of adaptive neuromodulatoon across animal nervous systems.

Beyond Reward: Reframing Octopaminergic Function in Associative Learning:-

For many years, the dominant interpretation regarding octopamine function in insect neuroscience revolved around a relatively simple conceptual framework where octopamine encoded for appetitive reinforcement while dopamine mediated aversive learning. This dichotomous model provided an important foundation for early investigations regarding associative conditioning and significantly advanced the understanding of insect reinforcement systems. However, the growing body of molecular, physiological, and circuit-level evidence accumulated over the past two decades. This increasingly demonstrated that such framework is insufficient to explain the complexity and flexibility of octopaminergic modulation.

One of the most significant limitations of classical reward-centric interpretation is it's inability to account for receptor-specific and circuit-dependent variability (**Burke et al.,2012; Sabandal et al.,2020; Kim et**

al.,2013) in behavioral output. Multiple studies present today, demonstrates that octopaminergic signaling contributes not only for appetitive learning but it also mediates aversive reinforcement, motivational regulation, memory allocation, and adaptive behavioral prioritization. Therefore, the functional consequences of octopamine release is dependent mainly on the receptor subtypes, neural localization, intracellular signaling architecture, and physiological context, rather than simply being fixed on an intrinsic valence assignment. Such findings strongly argues against the interpretations according to which octopamine is dedicated as a "reward neurotransmitter".

The recognition that octopamine frequently operates via interactions with dopaminergic reinforcement circuits (**Burke et. al.,2012**) has further transformed the contemporary understanding of associative learning mechanisms. Rather than being functionally independent, octopaminergic and dopaminergic pathways cooperate within layered neuromodulatory networks that collectively shapes the reinforcement processing as well as the memory formation. In the mushroom body circuits, octopamine-dependent activation of dopaminergic neurons contributes towards appetitive memory encoding via receptor-mediated calcium and cAMP signaling pathways. Similarly, coordinated octopaminergic and dopaminergic interactions participates in balancing appetitive and aversive learning according to the environmental conditions and motivational states.

Thus transition from transmitter-centered models towards distributed reinforcement architectures reflects towards a broader conceptual shift within neuroscience. Behavioral adaptation is rarely dependent on the isolated signaling pathways. Instead, neural systems continuously integrates sensory inputs, internal physiological state, prior experiences, and environmental uncertainty together to generate flexible behavioral responses. Within this framework, octopamine functions as a dynamic integrator neuromodulator that is capable of coordinating multiple dimensions of behavioral regulations rather than only transmitting a singular motivational signal alone.

The influence of metabolic state on octopaminergic reinforcement processing (**Berger et al.,2024; Meschi et al.,2024**) particularly highlights the inadequacy of simplistic reward models. Hunger, glycogen availability, endocrine signaling, and energy demands all substantially alters the reinforcing properties of sensory stimuli and the persistence of associative memories. Octopaminergic pathways therefore participates in evaluating not only the external reward value but also the physiological relevance of behavioral outcomes to the organism's internal conditions. Such state-dependent modulation allows reinforcement systems to prioritize adaptive behavioral strategies under the fluctuating environmental and metabolic constraints.

Importantly, contemporary evidences also suggests that reinforcement systems must maintain behavioral flexibility even under competing motivational demands. During starvation, for example, insects must prioritize food acquisition while simultaneously preserving sensitivity towards harmful or threatening stimuli. Octopaminergic compensation within the aversive reinforcement pathways illustrates how the distributed neuromodulatory architectures dynamically rebalances behavioral priorities without fully suppressing the essential survival responses. These findings supports the interpretation of associative learning as an emergent property of the integrated network dynamics rather than segregated chemical coding.

The evolutionary diversification of octopamine receptor systems (**Yang et al., 2026**) further reinforces this interpretation. Receptor-specific signaling properties, differential intracellular coupling, and lineage-specific adaptations indicates that octopaminergic pathways remains highly flexible and evolutionary tunable. Such

plasticity likely enables insects to occupy distinct ecological niches by optimizing reinforcement sensitivity, motivational regulation, and behavioral specialization according to species-specific environmental pressures.

Reframing octopaminergic functions within this broader context has important implications for future researches. Rather than asking whether octopamine encodes "reward" or "punishment", future investigations may benefit from examining that how octopamine regulates reinforcement allocations, motivational salience, behavioral prioritization, and state-dependent plasticity across distributed neural circuits. Advances in connectomics, in vivo calcium imaging, optogenetics, receptor-specific manipulation, and computational modeling will likely provide increasingly refined insight into how neuromodulatory networks coordinates adaptive behavior in both insects as well as vertebrates.

Ultimately, octopaminergic signaling should be viewed not as a rigidly specialized reinforcement pathway but as a flexible and context-sensitive component of integrated behavioral control systems. The progression from the classical valence-segregation models toward dynamic network-based interpretations reflects a major conceptual evolution in insect neuroscience and provides a more comprehensive framework for understanding how the neuromodulators orchestrate associative learning and behavioral plasticity across changing environmental and physiological conditions.

Conclusion and Future Directions:-

Research on octopamine signaling has undergone substantial conceptual transformation over the past two decades. Earlier studies have established octopamine as a principal appetitive reinforcement mediator in insect associative learning. These studies also proposed a relatively simple dichotomous relationship between octopaminergic reward pathways and dopamine dependent aversive signaling. Although this framework initially provided an important foundation towards understanding insect reinforcement systems but recently accumulating molecular, physiological, and circuit-level evidences demonstrates that octopaminergic function extends far beyond dedicated reward transmission.

Contemporary findings reveals that octopamine operates through receptor-specific, circuit-dependent, and physiologically regulated mechanisms that dynamically shapes associative learning and behavioral plasticity. Interactions among octopaminergic and dopaminergic pathways within the mushroom body circuits supported the layered reinforcement architectures where behavioral valence emerges from distributed network activity rather than isolated neurotransmitter identity. Furthermore, octopaminergic modulation is strongly influenced by internal metabolic state, endocrine signaling, motivational demand, and environmental context, thus highlights its broader role in adaptive behavioral prioritization.

The growing recognition that octopamine contributes to both appetitive and aversive processes under specific circuit configurations, represents a major shift in the understanding of insect neuromodulation. Rather than functioning as a rigid "reward neurotransmitter", octopamine appears to coordinate reinforcement allocation, motivational salience, sensory valuation, and state-dependent memory regulation across interconnected neural systems. Such flexibility likely provides significant evolutionary advantages by allowing organisms to dynamically adjust their behavior according to fluctuating environmental and physiological conditions.

Comparative and evolutionary analyses further suggests that octopaminergic signaling may reflect conserved organizational principles shared across diverse nervous systems. Structural and functional parallels between insects octopaminergic pathways and vertebrates adrenergic modulation reinforces the value of insect models for investigating general mechanisms of neuromodulatory integration and adaptive behavior.

Simultaneously, receptor diversification and lineage-specific evolutionary adaptation demonstrates that the plasticity of aminergic signaling architectures shapes the species-specific behavioral specialization.

Despite considerable progress, several important questions remain unresolved. The precise mechanism through which octopaminergic and dopaminergic circuits coordinate reinforcement allocation across varying physiological states are still not very well understood. Similarly, the extent to which the receptor-specific signaling pathways contributes towards the context-dependent behavioral flexibility requires further investigations. Advances in connectomics, optogenetics, receptor-selective manipulation, single-cell transcriptomics, calcium imaging, and computational neuroscience will likely provide us increasingly detailed insights into the dynamic organization of reinforcement networks in the coming years.

Further research should also make us move beyond the reductionist transmitter-centered models and instead it will make us focus over understanding about how the distributed neuromodulatory systems collectively regulates behavioral adaptation. Investigating how octopaminergic signaling integrates metabolic information, sensory uncertainty, environmental stress, and prior experiences may helps us establish the broader theoretical frameworks that links reinforcement processing to adaptive decision-making across species. Such approaches may ultimately reveal conserved principles governing how the nervous systems prioritize behavior under complex and changing conditions.

In summary, current evidences supports a reinterpretation of octopaminergic signaling as a flexible and context-sensitive component of integrated reinforcement architectures rather than as a simple appetitive neuromodulator. This evolving perspective not only advances understanding of associative learning in invertebrates but also contributes to broader efforts to decipher the organizational logic of adaptive neuromodulatory systems across animal nervous systems.

Acknowledgement:-

The author sincerely acknowledges the guidance and academic support provided by their supervisor throughout the development of this review. The author also thanks the department and institution for providing access to scientific literatures and academic resources that contributed to the preparation of this manuscrip. No external funding was received for this work. The author declares no conflict of interest.

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