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Biogenic Amines in Shaping Mosquito Behavior: A Biomolecule having Pharmacological Significance

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ABSTRACT

Despite of the lots of control measures against mosquitoes, the prevalence of malaria, dengue fever and other mosquito borne diseases have reached at an alarming level. Continuous climate alteration and generation of insecticide resistance are the primary reason for the vector emergence. Thus, developing new molecular tools and unraveling unique molecular targets for designing of novel mosquito repellent are urgently needed. Here, in this review we have highlighted the functions of two unique biogenic amines of mosquitoes and other insects. Further, functional and structural characterization of these two amines, viz. octopamine and tyramine, and their respective receptor might accelerate the scheming of novel chemical molecule to minimize the mosquito population growth.

Keywords: Malaria; Population growth; Elimination program

INTRODUCTION

Mosquitoes are one of the potent carriers of many debilitating vector borne diseases and cause millions of death each year. Changing in the environmental conditions and increased insecticide resistance are posing a challenge to control the mosquitoes [1]. Despite of growing awareness of malaria elimination program, launched by WHO, still there are significant increase in the cases vector borne diseases such as malaria, dengue in recent years in India [2]. In this genomic era, a wide scientific community is engaged to unravel molecular basis of different aspects of mosquito biology, essentially needed if new molecular tools are to be developed rapidly. One of the key strategies may rely to disrupt the adult female mosquito-human exposure. Thus unlocking and identifying crucial/novel molecular factors regulating the complex host seeking and blood feeding behavior could be an important step to establish such innovative tools [3,4].

Behavior of any organism from lower to higher organism is not a simple and single event, but it is managed by a complex but beautifully orchestrated series of events [5]. Though higher animals took advantage of having multiple sensing organs *viz*. visual, smell, auditory etc., but the total insect community is solely dependent on their smelling power to initiate each of their behavior [6-8]. Behavioral initiation through detection of chemical odors is further shaped by the finely tuned nervous system [9]. Different neurotransmitters, their cognate receptors includes diverse a diverse nature of neuromodulators such a neuropeptides and biogenic amines which synergistically coordinate to configure the insect's behavior [10]. In case of blood feeding insects, the evolutionary force also gives them the specialty of having blood meal from vertebrate host, a unique behavioral response, tightly regulated by both internal physiological cum nutritional needs as well as by external stimuli [11-14]. In comparison with other blood feeding insects, mosquitoes take much attention for its disease transmission ability due to its opportunistic and unique nature of blood feeding ability which make them the most dangerous disease transmitting vector [15,16].

Like other insects, each behavioral response of mosquitoes *viz*. hosts seeking, feeding, mating, oviposition is tightly regulated by olfaction followed by neuronal decision making genetic abilities [11,17]. However, the rate of success heavily dependent on detecting information from the surroundings, analyzing and processing them for rapid

execution of targeted behavior [7]. The plasticity in shaping of each of these behaviors is locked in the type of neuro-signaling mechanism, well-coordinated by associated learning process [18]. Though, the role of classical neurotransmitters in relaying information in the nervous system relatively has well been studied in other insects but the crucial role of other neuro-modulators such as neuropeptides and small biogenic amines are yet to unraveled. Thus in this review we aimed to give some glimpse of current knowledge over biogenic amines and their role in neuro-mediated mosquitoes behavioral regulations.

SYNTHESIS OF BIOGENIC AMINES

Biogenic amines are evolutionary conserved molecule which not only function in neuro-signaling but also play crucial role in several physiological functions [19]. Most of amines are common in both vertebrates and invertebrates (Dopamine, serotonin and histamine), but some biogenic amines are synthesized preferentially in either vertebrate (epinephrine and norepinephrine) or in invertebrates (tyramine and octopamine) to perform some specialized physiological functions [20,21]. Three different amino acids are the source of synthesis of different biogenic amines through multiple enzymatic reactions [20]. Tyrosine acts as a raw material for the synthesis of dopamine in both vertebrates and invertebrates. In addition to that, invertebrates have specialized biochemical pathway for the synthesis of tyramine and octopamine from tyrosine itself [20]. Next, serotonin is synthesized from tryptophan and histidine is the source amino acid for histamine in both vertebrates and invertebrates [20]. Thus, targeting the insect's specific pathway for the synthesis of tyramine and octopamine and blocking the tyraminergic and octopaminergic receptors mediated signal transduction cascade by some chemical means may be one of the alternative strategy to manipulate vector population which also has the benefit of exemption of off-target effects [20,22].

Biological Functions of Biogenic Amines

Valuing the central role of biogenic amines towards managing complex behavioral responses, here we summarize and update the knowledge of the insect/mosquito specific biogenic amines functions.

Octopamine:

Octopamine is broadly distributed in the insect's nervous system where it is called "flight and fight hormone" due to its ability of stress management [23]. Previous literature indicated that octopamine may play crucial role in non-specific arousal system of insects, where it can judge the stressful situation and facilitate in decision making of either fight or to escape [24]. In the central nervous system, it involved in the desensitization of olfactory stimuli, facilitate learning and memory and thus affect the adaptation [25,26]. By modulating the behavioral responses to attractant (pheromone), octopamine alters the mood of the animal [20]. Apart from the neuro-olfactory regulations, it is also found to present in the non-neuronal tissues such as hemolymph, muscle fiber, sense organs etc. [20,27]. Octopamine manages energy metabolism and homeostasis when present in the hemolymph, by regulating the breakdown of sugars and lipids [27]. In the peripheral organ of neuromascular junctions it affects intramascular protein synthesis which is concomitantly regulate muscular rhythm [20,28]. Surprisingly, an availability of considerable number of evidences predicting octopamine functions in other insects, but its role is poorly analyzed in mosquitoes. Thus, unraveling the molecular functions and mechanism of octopamine in the behavioral regulations in mosquitoes might open new opportunities to develop novel control strategies for mosquitoes with minimal adverse effect on the environment [29].

Tyramine:

Though, tyramine is the precursor molecule of octopamine but it has a significant role in insect body and it is believed that both octopamine and tyramine functions antagonistically, actions similar to adrenalin and noradrenalin in vertebrates [20]. For example, behavioral response to attractive odor is mediated by octopamine whereas behavioral response to general odorants is facilitated by tyramine [20]. Previous study by Kutsukake et al. suggested that tyramine receptor mutation impaired the olfactory responses of fruit fly *Drosophila melanogaster*, and these mutant flies are unable to avid repellent odors [30]. Except that, both octopamine and its precursor tyramine are known to involve in the regulation of larval locomotory behavior aversively [20]. Increase in the tyramine level reduces the speed of larval crawling movement [31,32]. Tyramine also modulates the activity of peripheral muscle of the reproductive system and legs of insects [33]. In case of mosquitoes, the octopaminergic and tyraminergic signaling was found to be crucial for oviposition and egg melanization but the other behavioral and physiological regulations of tyramine is remains to unravel [22].

Dopamine:
Dopamine is an important multifunctional neuromodulator, neurotransmitter and neuro-hormone both in invertebrates and vertebrates. In invertebrates, it is reported to have functions in olfactory reception and was found to influence the age dependent retardation of olfactory sensitivity [20,34]. Dopamine also play crucial role under nutritional stressed conditions, where the sensitivity of dopamine receptor increases against sucrose under starvation [20,35]. Studies also suggest that the regulation of amount of sleep and wakefulness is tightly modulated by dopamine and associated. A recent study by Kanta Terao et al. suggested that the neurons that are sensitive to dopamine play pivotal role in aversive learning in crickets [36]. It also has role in locomotion, courtship and development [20]. In mosquitoes, dopamine is directly related to host seeking behavior where it was found that increase in dopamine level reduces host finding activity [37].

Serotonin:
Serotonin is other most abundant monoamines in the gastrointestinal tract but also distributed throughout the animal body where it plays crucial multifunctional role [38]. In may insects, including mosquito's serotonin neurons are found to innervate in the midgut and the crop where it regulates the movement of the food through the gut [38]. Increase in the level of serotonin in the hemolymph of insects showed a reduction in the meal size [20,38]. In addition to that, serotonin functions in co-ordination with glutamate and was found to elevate the heart contraction rate in the mosquitoes [39]. Serotonin was also found to influence the feeding behavior of larvae of *Ades aegypti* mosquitoes [40]. Apart from that, previous study showed that serotonergic neurons that are innervated on the salivary gland of mosquitoes play crucial role in the regulation of salivation [41,42]. Recently, serotonin was also found to regulate hemocyte mediated immune response of the caterpillar *Pieris rapae* [43].

Histamine:
In comparison with other insect's biogenic amines the role of histamine has not been studied in detail. It acts as major neurotransmitters that are released in the photoreceptor cells after light exposure [20]. It has a crucial role in the communication between interneurons. Thus, histamine is considered as a crucial molecule however its role in sensory transduction in the visual perception and maintaining the interneuron connections is yet to be elucidated [20].

Prerequisite for Analyzing the Pharmacological Aspects of Biogenic Amine
Biogenic amines are small biomolecules which initiated their functions after binding with their respective receptors. The biogenic amine receptors predominantly belong to GPCR family. The signal transduction cascade that is activated after binding of the amines with their cognate receptors either is mediated by the synthesis of cAMP or by elevating the concentration of Ca^{2+} ion that are present on a specific location [20]. From the current literature, it is plausible to propose that biogenic amines and their receptors coordinate synergistically in the regulation of neuronal signaling, both in peripheral and central nervous system. Though, the roles of five different biogenic amines were extensively studied in other insects but unraveling their crucial function is very much needed in mosquitoes (Figure 1).

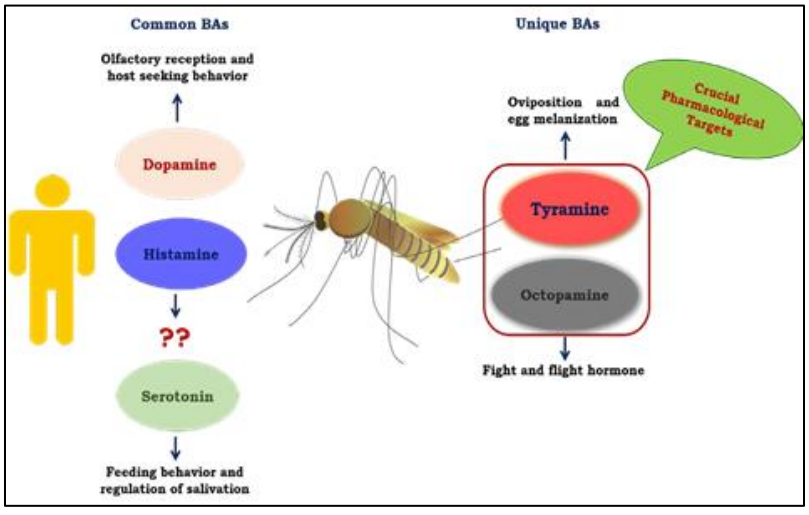

Figure 1: Schematic representation of the biogenic amines and their possible roles

Thus, the molecular characterization of biogenic amine receptors and their downstream molecules are prerequisite to design novel molecular tool for the management of diverse vectors including mosquitoes. Combination of experimental studies for function prediction analysis with the bioinformatics based structure prediction analysis coupled with the designing of novel chemical antagonists will not only improve our understanding of mosquito biology but also be an alternative strategy for mosquito control.

CONCLUSION

Dopamine, histamine and serotonin are the common biogenic amines in both vertebrates and invertebrates (mosquitoes), whereas tyramine and octopamine are insect's specific amines. Thus, octopamine and tyramine can be used as crucial molecular targets in future, for designing of novel chemical/pharmaceutical molecule to control mosquito population.

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