Chapter

Drosophila Central Taste Circuits in Health and Obesity

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Abstract

When there is a perturbation in the balance between hunger and satiety, food intake gets mis-regulated leading to excessive or insufficient eating. In humans, abnormal nutrient consumption causes metabolic conditions like obesity, diabetes, and eating disorders affecting overall health. Despite this burden on society, we currently lack enough knowledge about the neuronal circuits that regulate appetite and taste perception. How specific taste neuronal circuits influence feeding behaviours is still an under explored area in neurobiology. The taste information present at the periphery must be processed by the central circuits for the final behavioural output. Identification and understanding of central neural circuitry regulating taste behaviour and its modulation by physiological changes with regard to internal state is required to understand the neural basis of taste preference. Simple invertebrate model organisms like *Drosophila melanogaster* can sense the same taste stimuli as mammals. Availability of powerful molecular and genetic tool kit and well characterized peripheral gustatory system with a vast array of behavioural, calcium imaging, molecular and electrophysiological approaches make *Drosophila* an attractive system to investigate and understand taste wiring and processing in the brain. By exploiting the gustatory system of the flies, this chapter will shed light on the current understanding of central neural taste structures that influence feeding choices. The compiled information would help us better understand how central taste neurons convey taste information to higher brain centers and guide feeding behaviours like acceptance or rejection of food to better combat disease state caused by abnormal consumption of food.

Keywords: Taste, neural circuits, pharynx, gustatory receptors, feeding behaviour

1. Introduction

The sense of taste is a fundamental sensory modality for all animals. It controls many behavioural decisions by processing and integrating information from the periphery. In all animals, gustatory system plays a critical role in evaluating the nutritional value of food. The sense of taste warms animals against consumption of spoiled/fermented or toxic compounds and orchestrate appetitive responses to energy, protein and calorie-rich food sources.

In humans, taste buds on the tongue can differentiate between the five basic tastes: sweet, sour, salty, bitter, and umami (a savoury taste) by processing the taste information in the brain. These are important building blocks for our understanding of flavour. Animals show attraction towards low salt, sweet and umami taste

and aversive behaviour towards high salt, bitter and sour foods. Such responses are innate and largely invariant throughout animal's life suggesting physiological hard-wiring of taste quality to hedonic value.

For decades, flies have been used as a genetically accessible system to study molecular mechanisms that coordinate feeding behaviour with sensory signals. They show an array of feeding characteristics that can be easily exploited for various behavioural and physiological analysis. Identification of gustatory chemosensory receptors has provided a major impetus in understanding taste signal transduction [1–5]. Gustatory sensory neurons located in external mouth region as well as internally in the pharynx project to sub esophageal zone (SEZ-a region implicated in feeding and taste) [5–8]. Much less is known about the organization of the SEZ. Very few neurons that connect SEZ to higher brain centers have been identified. These circuits represent critical higher-order features of gustatory system including various set of interneurons, projection neurons, modulatory neurons and motor neurons that help flies to process and integrate peripheral taste signals. Although recently, many studies have focused on understanding how gustatory neural circuits are spatially organized to represent information about taste quality. Yet, the role of various regions in the central nervous system (CNS) in integrating feeding behaviour with sensory signals on the availability and quality of nutrients is currently insufficiently understood. How central taste circuits play an important role in health and disease is still undetermined. In this chapter, we have assimilated the information together to present a map of various taste circuits identified in the past few years beyond the level of primary taste neurons specifically in *Drosophila melanogaster.* Hopefully the information provided in the chapter would be useful to gain insight into brain structures and the neural networks that control taste and feeding behavior in simple model organisms and may provide information that would be useful in combating obesity or other metabolic disorders in humans.

2. Central taste circuits in humans

Tongue is the peripheral taste organ of the human taste system essential for tasting, chewing, swallowing and speech [9–11]. Tiny bumps present on the tongue called papillae give the tongue its texture. Many thousand taste buds cover the surfaces of the papillae that respond to taste and transmit that information from periphery to the CNS [9]. Different types of papillae are present on the tongue classified as circumvallate, fungiform, filiform and foliate. All except the filiform papillae are associated with taste buds. The most common mushroom-shaped fungiform papillae cover two third of the tongue and are involved in detecting taste. They also contain sensory cells for detecting touch and temperature. The human taste system, along with the olfactory and trigeminal systems, helps in identifying and controlling the nutrient versus toxic compounds that finally leads to acceptance and rejection behaviour [9, 12]. Inside the mouth, the chemical components of food interact with taste receptors cells located inside the taste buds on the tongue and evaluate the quality and intensity of the taste. The other areas where taste cells are present includes the back of the throat, and at the junction of the hard and soft palates, epiglottis, the nasal cavity, and even in the upper part of the esophagus [13, 14]. The current findings also suggest nutrient sensing and presence of taste receptors in the gut [15–18].

Taste buds are generally present as clusters of 50-100 polarized neuro-epithelial cells which can detect nutrients and other chemical compounds. They have

numerous sensory cells that are in turn connected to many different nerve fibres [12, 19]. The first stage of gustatory signal processing starts with the taste buds. They communicate using electrical coupling via gap junctions and by cell to cell chemical communication via neurotransmitters including glutamate, serotonin, and ATP among other possible transmitters [20, 21]. Taste receptor cells get consistently replaced in taste buds to compensate the injury of the gustatory epithelia [22]. Several afferent nerves carry specific sensory information from a specific peripheral region. The chorda tympani (CT), a branch of the facial nerve (cranial nerve VII), transmits gustatory information from fungiform papillae, while the lingual branch of the trigeminal nerve (cranial nerve V) carries information from fungiform about pain, tactile, and temperature and filiform papillae in the same area [23, 24]. Multimodal information including taste, tactile, pain, and thermal cues get conveyed from circumvallate papillae by the glossopharyngeal nerve (cranial nerve IX), from palatal taste buds by the greater superficial petrosal nerve (GSP, another branch of VII), and from the throat by the superior laryngeal branch of the vagus (cranial nerve X) [25–28]. Foliate papillae are innervated by the CT (taste) and V (tactile) in anterior regions and by IX (multimodal) in posterior regions [29, 30]. All together taste and oral somatosensory cues combine centrally with retro nasal olfaction to generate the composite experience of taste [31].

The entire human taste system includes both peripheral receptors and central pathways. As afferent taste signals ascend the brain from caudal to rostral, the information flow split between the ventral forebrain and more dorsal thalamocortical regions where primary and secondary gustatory cortices (opercular, insular, orbitofrontal) give rise to conscious taste sensation [32–34]. Taste qualities, attention, reward, higher cognitive functions and multiple-modal sensory integration are managed by multiple secondary and tertiary cortices that are involved in the dorsal pathways [20, 35, 36]. While sensory processing at the extent of the taste bud is complex, the information transfer to the CNS via marked line [37]. A gustotopic map has been produced when taste signals extend to the insula of the gustatory cortex [38]. Each individual taste has a representation in the insular cortex by fine-tuned cells organized in a precise and spatially ordered taste map with each taste quality encoded in its own stereotypical cortical field [38].

The final step in perceiving taste is relaying the taste information collected by taste cells to the central nervous system via cranial nerves VII (Facial), IX (Glossopharyngeal), and X (Vagus), where there is a topographical representation of the oral cavity within the first nuclear relay, the solitary tract nucleus, in which brainstem reflexes of acceptance and rejection are controlled (**Figure 1**) [39]. The taste cells within the taste buds transduce the stimuli from the ingested food and provide additional information about the identity, concentration and pleasant or unpleasant quality of the substance [20]. Taste nerve fibers on stimulation by the binding of chemicals to their receptors, depolarize, resulting in an action potential that gets ultimately transmitted to the brain [19]. This information also prepares the gastrointestinal system to receive food by causing salivation and swallowing (or gagging and regurgitation if the substance is noxious). The principal receptors involved to transduce human sweet stimuli are T1R2/T1R3, T1R1/T1R3 for umami stimuli (although mGluR1, mGluR4 and NMDA have been implicated), and T2R family for bitter taste stimuli. Growing evidences have suggested the role of epithelial sodium channel (ENaC) in part, in transducing salty taste, and acid sensing ion channels (ASICs) for sour taste stimuli [20, 40–42].

The ventral pathways are involved in autonomic and visceral functions, affective and emotional processing, memory and learning [43, 44] and ultimately, the

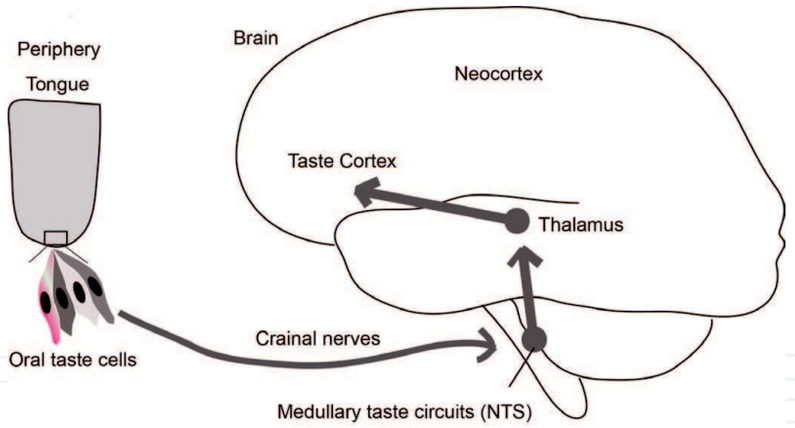

Figure 1.
A portion of the taste pathway in the human brain. Taste information from taste receptor cells on the tongue (peripheral organ) is relayed to the nucleus of the solitary tract (NTS) in the medulla. Gustatory neurons in the NTS send projections to the thalamus, which in turn directs gustatory information to taste cortex in the brain.

informational content and values of the ventral and the dorsal pathways integrate [45]. The circuitry is such that the cells make synaptic connection with primary sensory axons that run in the chorda tympani and greater superior petrosal branches of the facial nerve. The taste cells in fungiform papillae on the anterior tongue are innervated exclusively by the chorda tympani branch of the facial nerve. In circumvallate papillae, the taste cells are innervated entirely by the lingual branch of the glossopharyngeal nerve and in the palate they are innervated by the greater superior petrosal branch of the facial nerve [46]. The lingual branch of the glossopharyngeal nerve and the superior laryngeal branch of the vagus nerve project into the rostral portion of the nucleus of the NST. The central axons of these primary sensory neurons in the respective cranial nerve ganglia project to rostral and lateral regions of the medulla [47, 48]. Secondary cortical taste area in the orbitofrontal cortex, present in the frontal lobe of the brain is responsible for decision making [49]. Here, single neurons respond to combinations of chemosensory, somatic sensory, olfactory, and gustatory stimuli and even visual information [34]. Information about the temperature and texture of food transmit from the mouth via the cranial nerves to the thalamus and somatic sensory cortices [50].

In the orbital cortex, feeding to satiety with one food reduces the responses of those neurons to that particular food only suggesting computation of sensory-specific satiety in the orbitofrontal neurons [51]. Hypothalamic nuclei project to and receive input from other extra hypothalamic brain regions such as the nucleus of the solitary tract (NTS) to regulate food intake and energy expenditure [52–58]. Hunger, satiety and food consumption neural regulations are directly control by the genetic influence on human obesity [34]. High sweet tastes are attractive while high bitter tastes are aversive, even in decerebrate animals and anencephalic humans [59, 60]. The brain ascent from caudal to rostral by the afferent taste signals where the information start breaking between the ventral forebrain and more dorsal thalamo-cortical regions then later opercular, insular, orbitofrontal (primary and secondary gustatory cortices) bring the awareness to taste sensation [32].

Taste pathways in the CNS are intimately connected with general viscero sensory sensory nerves from the cardiovascular, respiratory and, importantly, gastrointestinal systems [61]. Circulating metabolic signals modulate neural responses in relays of the taste system, such as the NTS, and in areas that receive direct or indirect gustatory afferents like the hypothalamic homeostatic centers and reward-related

areas in the midbrain [62]. Vagus in particular contain afferent neurons that transfer mechanical and chemical sensory information from the gastrointestinal tract (GIT) to the brain. The neural transmission of chemical information could result from recognizing signalling peptides, such as CCK, produced by enteroendocrine epithelial cells with chemo-sensing properties [63].

Although a great deal of information has been generated but elucidation of how taste intensity is encoded in the insular cortex is necessary to address. It is still unknown whether taste qualities with similar valence project to common targets in the brain. Tracing the connectivity of each basic taste qualities to higher brain areas is still incomplete and will help decipher how these integrate with other modalities and combine with internal and external state for the final behavioural output. Hopefully understanding taste circuits in simple invertebrate model systems like *Drosophila* can help addressing these mysteries of the central taste system in higher animals.

3. *Drosophila* gustatory system and circuits

In the olfactory system of the adult fruit fly, the structure and function of the neural circuits involved in detecting and processing olfactory information are well known. Approximately 50 different classes of olfactory receptors neurons express a particular type of olfactory receptor. The olfactory sensory neurons expressing the same receptor projects its axon to a single glomerulus in the antennal lobe of the fly where synaptic association with projection neurons and local interneurons occurs. The projection neurons transfer processed sensory information from the glomeruli to higher order brain centers including mushroom bodies (MB) and lateral horn (LH) which further process olfactory information for behavioural functions such as learning and memory or appetitive and inhibitory response control [64–66].

On the other hand, the identified central taste circuits of the gustatory system of *Drosophila* involved in sensory processing i.e. from detection to behavior are very few. The gustatory system of *Drosophila* is a commendable system for learning taste perception, taste modulation and behavior due to its simple brain architecture of the fly, gustatory receptor neurons (GRNs), vigorous behavioural responses that are flexible to probe molecular genetics and electrophysiological dissection [67]. Different aspects of feeding behavior include finding a food source, evaluating food for nutritional suitability, choosing between different food sources, and deciding to initiate or terminate feeding. Like mammals, taste helps *Drosophila* to detect the potential edible food sources and to decide whether to accept it or not. The fruit fly can detect and sense all the distinct taste modalities that mammals can i.e., sweet, bitter, salts, water, sour and umami. Flies attract to sweet substances and show aversive behavior towards bitter making final feeding decisions [68]. The taste neurons house inside the hair like structures known as sensilla (**Figure 2B**) present on different peripheral organs of the fly body i.e., labellum, legs, wing margins, ovipositor and pharyngeal organs lining the esophagus (**Figure 2A**). The small sensory structures known as taste pegs are also present in the labellum [69]. Taste neurons of tarsal segments are the first that come in contact with food source and then on the labellum (**Figure 2A**) [70]. The GRN axons from various peripheral taste organs transmit the taste information to the higher brain area, the primary taste processing center called SEZ (**Figure 2A**) [71]. SEZ is the first relay for taste information in the fly brain just below the antennal lobe where axons of gustatory receptor neurons (GRNs) of peripheral organs terminate [67, 72, 73].

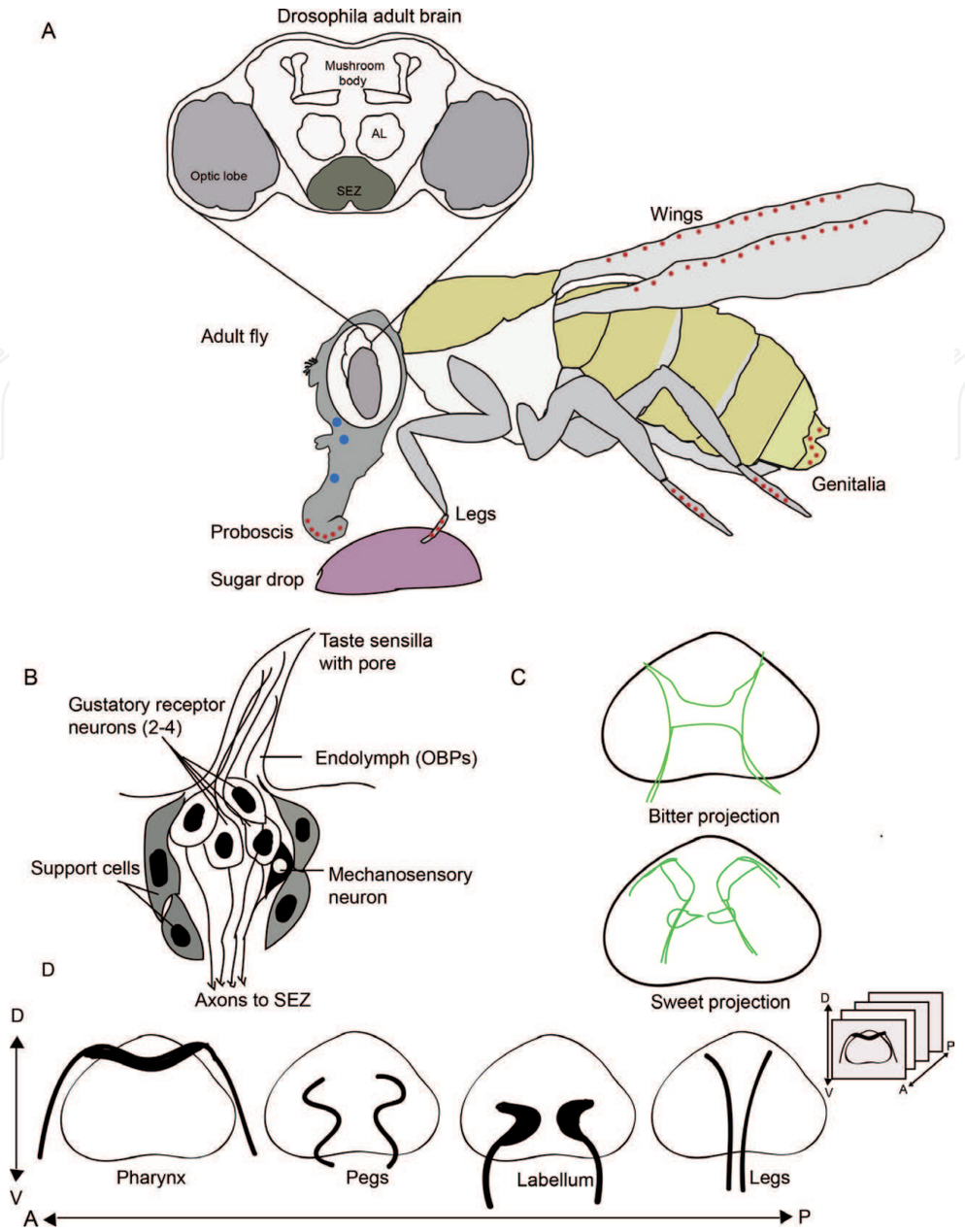

Figure 2.
Drosophila *taste system. (A) Adult fly accessing sugar drop with the tarsi. Proboscis, legs, wing margins, and genitalia are peripheral taste organs where taste receptor cells house in taste sensillae. The taste information from various taste organs goes to the brain. SEZ is a first relay of taste processing (shown in the magnified version of brain). Antennal lobe (AL) receive information about volatile chemicals from the periphery and mushroom bodies are learning and memory centers. (B) Taste sensillum containing gustatory receptor neurons, mechanosensory neurons and support cells. (C and D) Taste representation in the SEZ. Projection map in the SEZ in accordance with the taste modalities (C) and taste organs (D).*

4. *Drosophila* SEZ is the first relay of taste information

The adult *Drosophila* bears approximately 135,000 neurons in the central nervous system and thousands of neurons in ventral nerve cord (alike mammalian spinal cord). Taste neurons transmit their input (**Figure 2B**) to SEZ in the CNS, where the inputs received from different organs and taste modalities are refined and united [74] (**Figure 2C** and **D**). The gustatory neuropil of the SEZ includes the sub esophageal zone, gnathal ganglia (GNG), and parts of the periesophageal neuropil [75], and is relatively disorganized compared to the olfactory and visual neuropils. Immunohistochemistry and microscopy visualization of axonal termini of distinct

categories of GRNs has exposed a spatial representation of taste quality within SEZ for example sweet taste neurons from proboscis terminate in discrete regions of the SEZ that do not overlap with axonal projections of bitter taste neurons (**Figure 2C**) [67, 72]. There is a distinct projection map in the SEZ in accordance with the taste modalities (**Figure 2C** and **D**) [67, 72] and taste organs i.e. gustatory axons of the mouth part ends in the dorsal anterior SEZ, axons from labellum ends in the medial SEZ, and axons from legs ends in dorsal posterior SEZ (**Figure 2C** and **D**) [67, 71]. Motor neurons and modulatory neurons that guide proboscis extension are also found in the SEZ [71, 76] indicating that the SEZ carry local circuits that connect sensory, motor, modulatory and command neurons that have processes in this region [71, 76–78] suggesting its role as a sensorimotor center for feeding. Taste information is also integrated with other internal and external sensory cues, but where this occurs is not known. Later the taste information get conveyed to higher brain centers, including the mushroom body, which contains neurons activated upon sucrose ingestion [79, 80]. Recently found various central neurons that may or may not synapse with taste sensory neurons and/or play modulatory roles have been identified which are discussed in further sections.

5. *Drosophila* sweet taste feeding circuits in the brain

SEZ has been shown to play a key role in gustatory signal transduction and feeding responses in different insects. *Drosophila* larval neurons expressing neuropeptide gene (referred as *hugin* neuron) are identified as probable interneurons that modulates taste mediated feeding behavior [77]. These are about 20 neurons in the SEZ. The connectivity pattern of *hug* neurons in larvae and adult flies is similar. Blocking *hug* neurons activity results in alteration of food intake initiation which depends on previous nutrient condition. The *hug* neurons send axons to three distinct targets - to the ring gland (central neuroendocrine organ), pharyngeal muscles, and higher brain center protocerebrum. The extension to the ring gland and the pharyngeal muscles depicts that *hug* neurons correlate sensory information with growth, metabolism, and feeding. The axon tracts to the protocerebrum indicates a role of *hug* neurons in transducing sensory signals for higher brain processing. The connectivity pattern of *hug* neurons suggest a role of incorporating gustatory sensory signals with higher brain functions and feeding behavior [77].

Additionally, to understand the central taste circuits in the fly brain that are involved in feeding decisions and different aspects of feeding behavior few second order neurons have been identified in the past few years. The first set of sweet gustatory projection neurons (sGPNs) marked by *NP1562* have been identified in a genetic screen (**Figure 3A**) [81]. Suppression of sGPNs activity results in decrease food intake and inhibition of PER responses. The sGPNs activation by applying sucrose and other sugars to the labellum suggested a functional link with Gr5a+ sweet taste neurons. These neurons relay sweet information from the SEZ to the antennal and mechanosensory motor center (AMMC) in the deutocerebrum of fly brain. Starvation and dopamine signaling increases the sucrose sensitivity of the sGPNs providing direct confirmation for state dependent alterations in sweet taste circuit activity [81]. The AMMC is known to receive input from sensory axons of the basal antennal segments involved in sensing gravity, sound and [82–85] olfactory inputs from a class of olfactory projection neurons [86]. It remains to determine if AMMC acts as a secondary center for sweet taste and receive inputs from other categories of taste neurons, such as water [87, 88], bitter [67, 72], and salty [89, 90], sour [91] and fat [92] and, if so, whether the representation of different tastes remains distinct in AMMC. Little is understood about the wiring where information from the AMMC is transmitted, but single-cell tracing experiments in

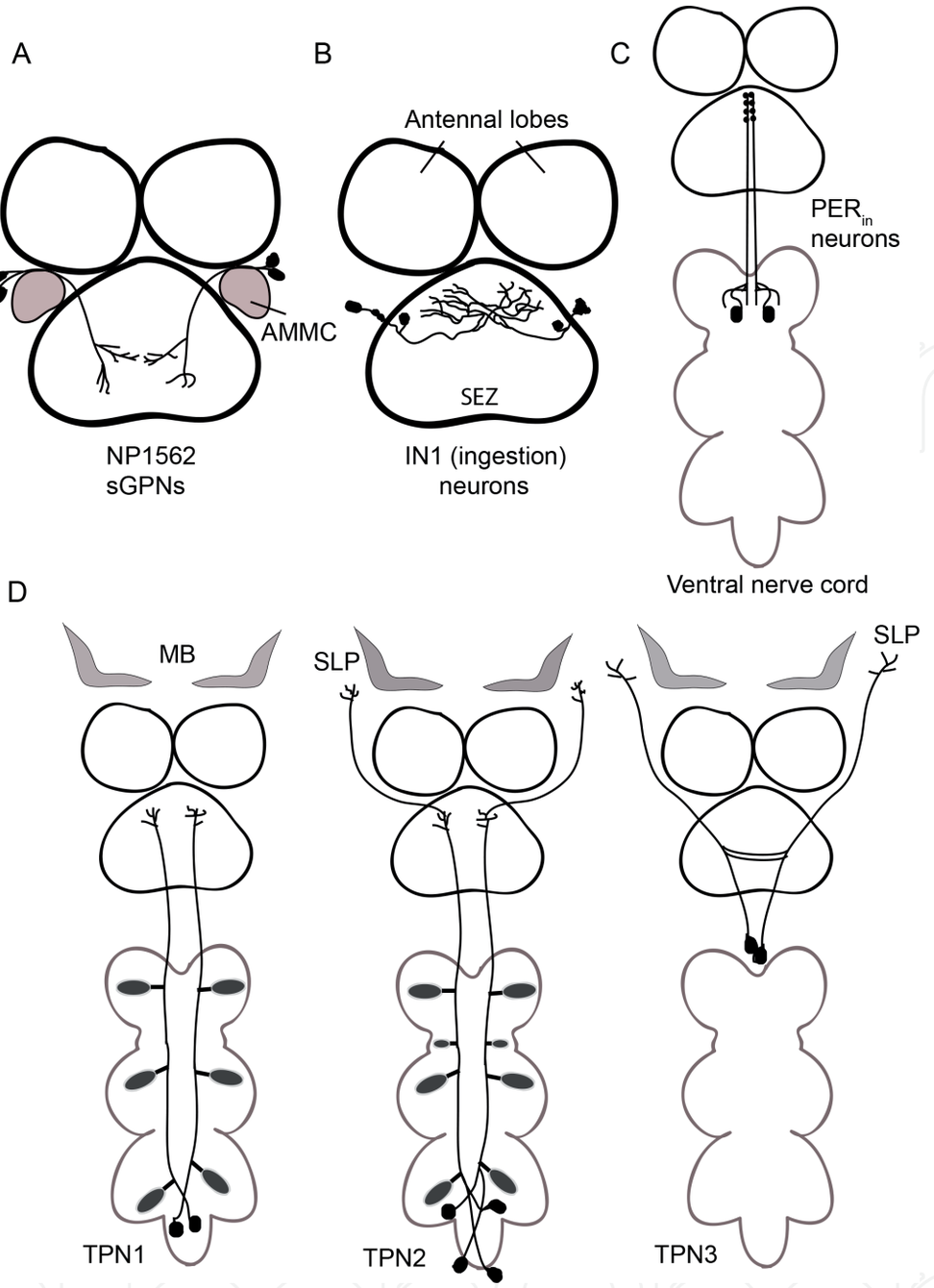

Figure 3.
Examples of few taste circuits in the Drosophila *brain. (A) Sweet gustatory projection neurons (*NP1562+ *sGPNs). (B) IN1 Cholinergic Local Taste Interneurons (ingestion neurons). (C) PER$_{in}$ neurons. (D) TPN1, TPN2, TPN3 neurons. TPN2 and TPN3 neurons terminate in the SLP (superior lateral protocerebrum) and in and around lateral horn area. Both SLP and lateral horn are nearby structure.*

flies reveal the caudal ventrolateral protocerebrum (CVLP) as a possible target [93] as some Gr32a+ GRNs involved in pheromone sensing appear to terminate directly in the VLP [94]. It is still undetermined whether AMMC conveys information from sGPNs to higher brain centers or back to the SEZ, where it can be transferred to motor neurons connecting to proboscis muscles.

Another genetic screen identified pair of 12 cholinergic local interneurons to characterize *Drosophila* ingestion circuit. These neurons namely IN1 (ingestion neurons, **Figure 3B**) controls the dynamics of ingestion in flies regulated by hunger state and sucrose concentration [95]. Upon sucrose ingestion, IN1 interneurons show persistent increase in activity in fasted flies. The activity drops in response to subsequent feeding bouts. Conversely IN1 interneurons in fed flies show smaller responses to sucrose which lacked persistent activity. In a satiated fly, insensitive

sucrose IN1 neurons show decrease drive to ingest and results in shorter ingestion episodes. IN1 SEZ second-order interneurons monitor ingestion by receiving pre-synaptic input from sugar sensitive taste neurons in the pharynx [95]. Hence, the IN1 probably be the second- order neurons for a particular subprogram of feeding behavior i.e. ingestion that provides a fast feedback mechanism to regulate sucrose ingestion by integrating taste and hunger signals. The study proposes IN1 neurons as a key node in the circuit that governs rapid food intake decisions.

6. Bitter taste circuit in the brain

The bitter taste modality is conserved in insects and mammals. It plays a key role in evoking aversive behavior in animals [32, 66, 68, 96]. Bitter sensitive gustatory interneurons (*VGN6341*) in the adult SEZ are identified by performing a functional behavioural screen and shown to be involved in aversive gustatory responses [97]. These neurons receive direct synaptic input from *Gr66a* labelled bitter-sensitive GRNs. The *VGN6341* neurons are single bilaterally symmetric pair of SEZ interneurons responsible for the inhibition of the appetitive PER responses and gets activated by natural or transgenic stimulation of bitter GRNs [97]. Identified bitter gustatory local interneurons (bGLNs) play an important role in the aversive bitter-sensitive gustatory circuitry of the adult fly and represent a significant step towards understanding how bitter taste modalities are processed by the gustatory circuitry in the brain. Identifying their postsynaptic targets in the bitter gustatory circuitry of the SEZ will reveal new players of the bitter higher order taste circuits. And whether they will receive excitatory or inhibitory input from these new player's cells await further investigation [97].

Three classes of taste projection neurons (TPNs) have been identified based on their morphology and taste selectivity [98] named as TPN1, TPN2 and TPN3 (**Figure 3D**). TPN1/TPN2 neurons respond to sweet taste and promotes PER (innate feeding behavior) while TPN3 is bitter responsive and inhibits PER. TPNs are long-range projection neurons that separately carry sweet (TPN1 and TPN2 selectively relay sugar taste detection from the legs) or bitter information to higher brain demonstrating modality-specific relays. TPN3 responds to bitter taste on the legs and the proboscis, suggesting aversion to bitter compounds may not require specific location. Their data suggests that taste detection from different organs serves different functions, consistent with other studies where interneurons sense sweet taste from the mouthparts and drive ingestion [95]. The organ-specific and modality-specific connectivity of TPNs demonstrates a mechanism to encode both taste location and taste quality. As both TPN2 and TPN3 send axons to the superior lateral protocerebrum (SLP) (**Figure 3D**) suggesting that information from the higher brain feeds back onto sensorimotor circuits for PER. Functional link from TPNs to mushroom body (learning and memory centers) has been postulated based on the presence of their arbors in the SLP and lateral horn, which further excite or inhibit MB extrinsic neurons. Reciprocal and bidirectional interactions between SLP and MBs for learned associations have also been shown previously [99]. Conditional silencing of TPNs suggested that TPNs are not essential for proboscis extension and contribution from other neurons must contribute to this behavior but TPN2 and TPN3 are essential for conditioned taste aversion. Inhibition of synaptic transmission in sugar-sensing TPN2 during either training or testing decreased conditioned aversion, whereas inhibiting bitter TPN3 decreased aversion only if inhibition occurred during training. The modulatory role played by TPNs without being essential components of PER circuits require future investigation. These studies demonstrate modality-selective taste pathways to higher brain.

In a separate study, a pair of interneurons (PER_{in} neurons, **Figure 3C**) are identified that activate by stimulation of mechanosensory neurons inhibiting feeding initiation. Conversely, inhibition of activity promotes feeding initiation and inhibits locomotion suggesting such neurons suppress feeding while the fly is walking [100]. The dendrites of these neurons reside in the first leg neuromeres whereas axons are found in both SEZ and first leg neuromeres suggesting that they process information from the legs and convey to SEZ. These neurons do not make synaptic connections with known neurons that regulate proboscis extension. This study highlights that feeding initiation and locomotion are mutually exclusive behaviours and identified pair of interneurons influence this behavioural choice.

A receptor-to-neuron maps of pharyngeal taste organs reveals the presence of multiple classes of taste neurons [101], consistent with the knowledge that the pharynx may independently assess food quality. In this study use of *Pox-neuro* (*Poxn*) mutants (mutants in which all external taste bristles are transformed into mechanosensory bristles but all pharyngeal taste neurons retain) [101–104] suggests how pharyngeal taste input affects feeding behaviours. It is found that high salt inhibits sucrose-evoked activity of pharyngeal *Gr43a+* sweet GRNs. Furthermore, feeding avoidance of denatonium, tartaric acid, or high salt eliminates only when both inhibition of pharyngeal *Gr43a* sweet GRNs and activation of different combinations of aversive pharyngeal GRNs are absent. Tracing experiments reveals that both appetitive and aversive pharyngeal GRNs convey inputs to two common brain areas (pars intercerebralis and lateral protocerebrum), suggesting that pharyngeal taste is represented across brain regions. This study demonstrates an important role of pharyngeal taste in controlling food choice and intake [105].

7. Central neurons controlling regurgitation

In another genetic screen to understand how sensory information is translated into behavior, a subset of higher order neurons labeled by *VT041723-GAL4* transgenic line are identified that controls regurgitation after food ingestion [105]. The neurons labeled by *VT041723-GAL4* receive sensory input from peripheral *Ir76b+* taste neurons in the pharynx. Optogenetics activation of these neurons produce "proboscis holding" behavior (extrusion of the mouthpart without withdrawal). Flies pre-fed with either sugar or water before neuronal activation shows regurgitation indicative of an aversive response. However, motor circuits controlling regurgitation and if PER and regurgitation share common motor programs are not known. Identification of *VT041723-GAL4* neurons provide a ground to address such questions [105].

8. Higher order taste circuits involved in taste learning and memory

In *Drosophila*, MBs are the central sites for experiential learning that are composed of approx. 2,000 Kenyon cells (KCs) which have dendrites in a region known as calyx (**Figure 4A**) [106–108]. Pairing of sugar with a deterrent compound creates aversion to sugar in flies although for the short duration [109]. The conditioned taste aversion involves MBs [80, 109]. How the diversity of sensory information that the MB integrates is still undetermined. Anatomical studies have suggested that visual, tactile and gustatory cues are processed in different compartments of MB as conditional stimulus (CS) [110]. The MBs also receives multimodal inputs as they are required for courtship, taste conditioning and visual learning [109, 111].

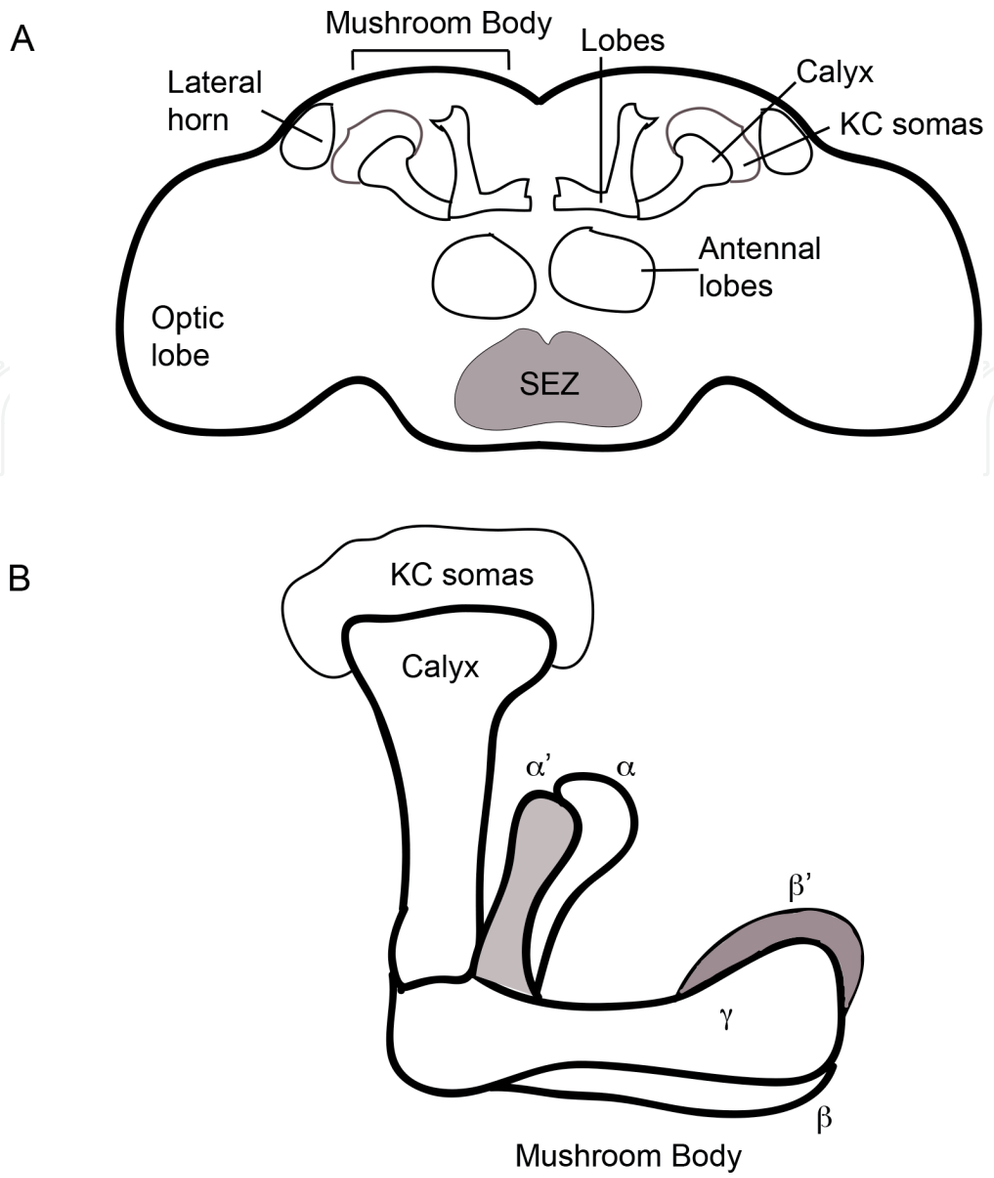

Figure 4.
Adult Drosophila *brain showing higher brain areas. (A) Learning and memory centers in adult fly brain includes mushroom body, calyx, Kenyon cells (KC) and lateral horn. (B) Structure of MB lobes. There are three different classes of neurons that make up the MB lobes (α/β, α'/β' and γ).*

Based on their axonal arborizations in the α/β, α'/β', and γ lobes, the KCs of the MB are divided into three main classes (**Figure 4B**). Evidences have identified that functional specializations among and within the classes, with different subsets playing different roles in the phase, type, and length of associative memory [112]. Evidence that the MB processes tastes as CS and US (unconditional stimulus) comes from behavioural taste conditioning experiments [109, 113]. A simple taste behavior is the proboscis extension response (PER): when leg gustatory neurons detect sucrose, the fly extends its proboscis to eat. Pairing sucrose stimulation to the leg (CS) with an aversive stimulus (US) causes short-term inhibition of proboscis extension. This learned behavior requires the MB, but the neural processing in the MB that underlies taste conditioning is unknown. To gain insight into sensory processing, taste representation and role of these structures in aversive taste conditioning in the MB, behavioural and high end imaging studies reveal that the gustatory information in the main calyx are segregated and have unique representation by different taste modalities and different taste organs [80]. Such inputs get differentially and independently modified by learning. Selectively blocking the γ lobe neurons

leads to complete elimination of conditioned aversion suggesting role γ lobe as the site for aversive taste memory formation in the MB. The study also demonstrates the requirement of MB neurons for taste conditioning and taste information relayed to the MB is via multiple pathways. Only taste stimulation (bitter compounds and sucrose) activates the dorsal accessory calyx which has been implicated in gustatory processing in other insects earlier [114] providing evidences that gustatory MB representation is distinct from olfactory cues. These studies have extended the understanding of the neural coding underlying conditioned learning in the MB as a sensory integration center in the fly brain.

9. Motor neuron circuit

Interneurons are the local circuit neuron of CNS that relays impulses between sensory neuron and motor neuron while a neuron that passes from CNS or a ganglion towards a muscle and conducts a nerve impulse resulting in movement is known as motor neuron. The process by which brain process the sensory information into motor actions is not well acknowledged. A major step in most of the sensory-motor transformations is to convert the coordinates of sensory system into a map of spatially directed motor actions.

Proboscis is the primary feeding organ of flies and also plays an important role for taste cue detection and food ingestion and show reliable PER by applying positive gustatory stimulus to GRNs [67, 109, 115, 116]. PER represents an innate, sequential behavior involving many movement steps [78]. PER sequence may require activation of different muscle groups at distinct time points, implying a defined temporal organization of upstream motor neuron (MN) activity. It has been proposed that the relay of gustatory sensory information from GRNs to MNs occurs mainly within the SEZ [67, 72, 117–119]. The motor neurons innervating proboscis musculature have been portrayed in fruit fly and blow fly [120, 121]. There are 15 paired proboscis muscles found in blowfly and 17 in *Drosophila*, illustrating 13 prime muscle groups. These muscles control action of 3 segments of the proboscis i.e. rostrum, haustellum and labellum with distinct muscles intricate in extension or retraction. The central and dorsal dilator muscle, forms the cibarial pump, which dilates the pharynx to coordinate fluid intake [122]. Twenty pairs of motor neurons innervate proboscis muscles [120, 121] and each proboscis muscle is innervated by 1 to 3 motor neurons. On the basis of the nerve through which their axons depart the CNS, the proboscis motor neurons are categorized as labial, pharyngeal, or accessory pharyngeal. The Cibarial muscles, forming the oral pump, are innervated by pharyngeal motor neurons, while the proboscis muscles required for the placement of proboscis during feeding are innervated by labial motor neurons.

A pair of neurons that generate feeding motor program and induces the entire feeding sequence when activated are identified in *Drosophila* [78]. The interneurons called feeding neurons (*fdg*) located in the SEZ are required for feeding as their suppression eliminates the sugar-induced feeding behaviour (**Figure 5B**). Activation of a single *Fdg*-neuron leads to asymmetric feeding behavior. *Fdg*-neurons respond to food only in starved condition suggesting this response is dependent on the metabolic state of the animal. The asymmetric regulation of proboscis extension by the *Fdg*-neuron suggests that each *Fdg*-neuron may selectively regulate the strength of proboscis muscle contraction on the same side of the body. These results are consistent with the observation that presentation of food to gustatory receptors on one side of the body leads to proboscis extension on that side demonstrate that *Fdg*-neurons operate firmly within the sensori-motor watershed, downstream of sensory and metabolic cues and at the top of the feeding motor hierarchy to execute

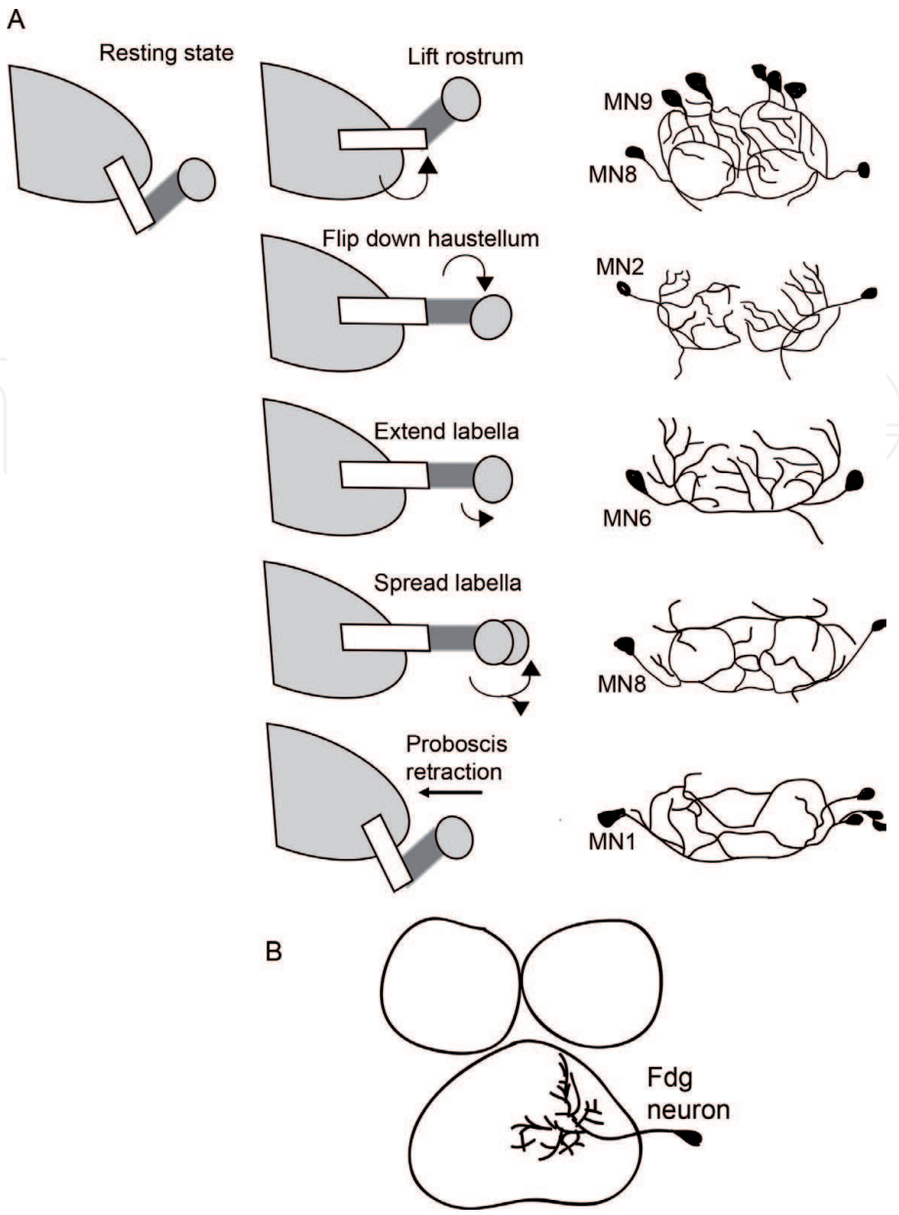

Figure 5.
Examples of motor neurons in adult fly that are involved in proboscis extension. (A) Five motor neuron types that control the key steps of proboscis extension were identified, lifting of the rostrum (MN9), extension of the haustellum (MN2), extension of the labella (MN6), spreading of the labella (MN8) and proboscis retraction (MN1). (B) Fdg *neurons.*

the decision to feed. How the *Fdg*-neurons coordinate the various motor patterns involved in feeding remains to be determined.

One of a study revealed that the mouth mechano-reception can ease and end feeding by two distinct central motor circuits and these two mechanosensory circuits merge with bitter taste in opposing manners to shape feeding behavior. Mechanosensory neurons (MSNs) were identified in taste pegs and taste bristles of the labella which rely on the same mechanoreceptor, NOMPC (No mechanoreceptor potential C) to transduce mechanical drift. The optogenetic arousal of bristle MSNs induce labellar spread, while activation of peg MSNs induces proboscis retraction [123].

Another pair of motor neurons involved in taste behavior has been identified to identify the components of the PER circuits. These neurons activate by sugar stimulation and inhibit by bitter stimuli [76]. The bilateral pair of E49 motor neurons are both necessary and adequate to initiate proboscis extension reflex. Although these neurons synapse on proboscics musculature and show wide dendritic field in SEZ but otherwise are shown to make no direct connections with GRNs [76].

In *Drosophila*, feeding is achieved by a pump that draws fluid into the esophagus. It has been shown that the cibarial motor neurons play a key role in such a pumping behavior [124]. The inhibition of these motor neurons decrease the feeding and pump frequency, while activation induce arrhythmic pumping. The rate of pumping is shown not to be affected by sucrose concentration or hunger but is changed by fluid viscosity. These neurons respond to taste stimuli and show prolonged prolonged to palatable substances. The open question is how cibarial pump motor neurons talk to rest of the feeding circuit in flies. How rhythmic motor activity is generated together with other feeding motor program such as proboscis extension and retraction and the neural circuits involved in such a behavior will provide insight in their role in the feeding circuit. There is a possibility that different chemosensory inputs may trigger PER and pumping as stimulation of tarsal taste neurons elicit PER but not pumping [115, 125]. Further studies revealed four GABAergic interneurons in the fly brain that impose feeding restraint in *Drosophila*. Inactivation of these neurons results in excessive ingestion of all compounds regardless of taste quality or nutritional state while severe activation of these neurons decreases ingestion of water and nutrients. These neurons act upstream of motor neurons for multiple feeding subprograms such as meal initiation and ingestion. Hence, this study unfolds how central inhibitory control regulates feeding behaviors and is required to inhibit a latent state of uncontrolled and nonselective consumption [125].

In a separate study, analysis of sequential features of the motion pattern of PER provided morphological description of proboscis motor neurons and muscles [121]. By implying genetic manipulations along with artificial activation and silencing process, five motor neuron types that control the key steps of proboscis extension are identified, lifting of the rostrum (MN9), extension of the haustellum (MN2), extension of the labella (MN6), spreading of the labella (MN8) and proboscis retraction (MN1) (**Figure 5A**). The above-mentioned steps are independently controlled in a one-to-one manner with the majority of MNs both sufficient and required for the execution of one individual step of the forward reaching behavior.

Remarkable specificity has been observed for candidate higher-order neurons in terms of the sensory neurons that activate them (proboscis versus mouthparts) and the behavioural subprograms they generate i.e. proboscis extension versus ingestion. The identification of these neurons suggest taste information is processed by parallel labelled lines via several different neural streams that coordinate different aspects of feeding behavior. Another behavioural study of the function of different taste neurons on the legs found that some cause inhibition of locomotion whereas others promote proboscis extension [72]. This study highlights that sweet taste receptor neurons of legs are essential for sugar choice and highlighted a functional dissociation between and within taste organs of *Drosophila*.

10. Modulation of feeding behaviors via taste circuits

Taste preference and sensitivity are two most essential elements of food evaluation. Such criteria are not always constant and often change depending on internal states such as hunger and satiety. Recent evidences reveal that starvation induces increased sweet taste preference and sensitivity at the periphery and in the CNS in various species from fruit flies to humans [81, 126, 127]. Electrical recordings of various neurons in central brain areas in mice and monkeys including amygdala, orbital frontal cortex, and hypothalamus have indicated the existence of neurons that can respond to taste stimuli in a state (hunger/satiety)-dependent manner [128–130]. However, the key neuronal pathway(s) responsible for hunger-induced taste modification are still unknown.

Neuromodulators such as neurotransmitters, neuropeptides, and endocrine hormones, play an important role in changing the morphological and functional characteristics of neural circuits to achieve behavioural flexibility. The changes in taste preference could occur through variation in the peripheral taste receptor cells, or in higher order neural circuits controlling food intake in the brain. To understand how changes in the internal state influence behavioural decisions in flies, various neurons in the SEZ whose activity depends on starvation state have been identified. It has been suggested that Dopamine is a potent modulator of a variety of behaviors in mammals and flies. Tyrosine hydroxylase ventral unpaired medial (TH-VUM) dopaminergic neurons modulate feeding in response to nutritional needs (**Figure 6A**) [131] and feeding (*Fdg)* interneurons (**Figure 5B**) integrate gustatory input with the internal state to command a feeding behaviour routine [78]. Even in mice mutant for Tyrosine hydroxylase show failure in initiating feeding in spite of intact motor ability to consume [132]. It has been shown that TH-VUM neurons can drive proboscis extension and neuronal activity of TH-VUM corresponds with the starvation duration. Silencing TH-VUM neurons decrease PER in starved flies to sucrose whereas increasing the activity of TH-VUM elevates PER in both fed and starved flies [131].

Role of various neuromodulators in regulating feeding responses in starved adult *Drosophila* [125, 133–135] has shown that dNPF and sNPF, neuropeptides related to mammalian NPY, modulate multiple feeding related behaviours, including the formation and expression of food-associated memory, enhancement of food-related olfactory sensitivity, and control of food intake during starvation [136–140]. During energy deficit conditions, animals become less selective in their food choices by enhancing their sensitivity to nutritious resources, such as sugar [115, 141–145]. Hunger enhances behavioural sensitivity to sweet taste, at least in part, via increased dopamine (DA) release onto Gr5a-expressing sugar-sensing GRNs, which increases calcium responses to GR activation in flies [131, 144]. Starvation also reduces sensitivity to unpalatable and potentially toxic compounds, such as bitter tastants. In PER assay, sensitivity to bitter tastants reduce in fasting flies', in part, independently of the increase in sugar sensitivity [126]. Both dopamine and dNPF^{+} modulates sugar and show enhanced sugar sensitivity during starvation. dNPF act upstream of dopamine to control sugar. This study also suggests that subsets of sNPF expressing neurons regulate bitter sensitivity under starvation and sNPF as well as dNPF-dopamine pathways independently regulate bitter- and sugar sensitivity at the neuronal circuit level suggesting neuromodulatory cascades serve as key mediators of state-dependent control [134, 146–148]. Separately it has been shown that starvation reduces Octopaminergic/tyraminergic OA-VL activity and results in depotentiation of bitter taste in flies (**Figure 6B**) [149].

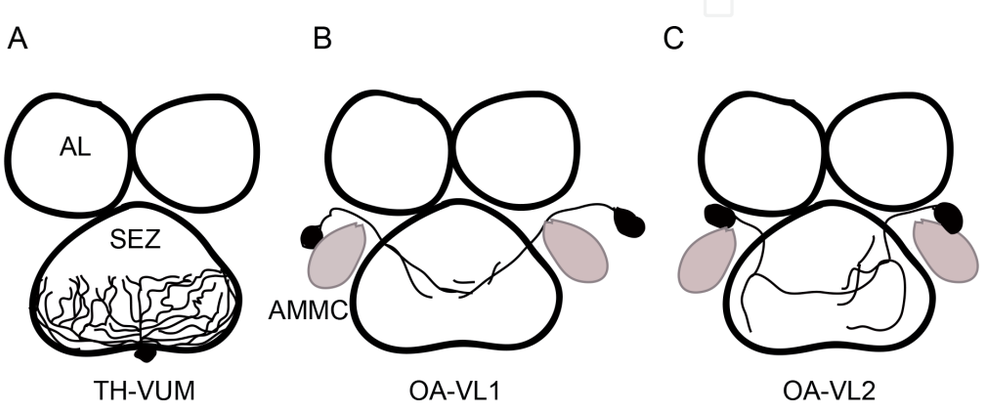

Figure 6.
Examples of few modulatory neurons in the adult fly brain. (A) TH-VUM neurons. (B) OA-VL1 and OA-LV2 (B) neurons that send projections to SEZ.

Recent identification of second-order sweet taste neurons [81] has enabled investigations into the interplay between sweet taste circuits and other sweet- and starvation responsive neurons to understand the neural basis of feeding behavior. Both starvation state and an increase in dopamine signaling brings about an enhancement of sGPN sensitivity to sucrose. In both cases, increases in sucrose-induced calcium activity occurs in the absence of corresponding changes in peripheral sweet Gr5a+ neural activity. Other studies have detected that starvation leads to increases in sucrose-evoked electrophysiological [150, 151] or calcium activity in Gr5a+ taste neurons [144]. In most cases, the observed increases in GRN sensitivity was comparatively small in magnitude compared with the alterations in *NP1562*+ sGPN activity of starved flies.

There are several other neurons that have been identified as modulating sugar feeding. A pair of *Fdg* (feeding) neurons (**Figure 5B**) act as command neurons in the fly, is also required for normal feeding behavior as the ablation of the neurons distort the sugar prompt feeding behavior. These neurons activate by sugar taste but only in starved flies [78]. Moreover, twelve cholinergic interneurons, IN1 in the SEZ form synapse with sugar sensing neurons. The activity of these neurons is also regulated by hunger state/starvation but unlike feeding neurons that respond to sweet taste, ingestion neuron is triggered by sucrose ingestion. Also, the activation of IN1 neurons increases the chance of sugar ingestion upon presenting a drop of sucrose solution in close proximity instead of directly triggering the feeding behavior [95].

In another study, it has been shown that only sweet neurons express $GABA_B$ receptor ($GABA_BR$) [152]. $GABA_BR$ mediates presynaptic inhibition of calcium responses in sweet GRNs, and both sweet and bitter stimuli evoke GABAergic neuron activity in the vicinity of GRN axon terminals. Blockage of $GABA_BR$ both lead to increased sugar responses and decreased suppression of the sweet response by bitter compounds. This study propose a model in which GABA acts via $GABA_BR$ to expand the dynamic range of sweet GRNs through presynaptic gain control and suppress the output of sweet GRNs in the presence of opposing bitter stimuli [152].

Further evidences [77] show that *hug* neurons function within a neural circuit that modulates taste mediated feeding behavior. Suppression of *hug* neurons activity, cause a change in particular feeding behavior response. As a result of this alteration the control flies when shifted to a new food medium, they hold back for a period of time before feeding, on contrary the experimental flies initiate feeding promptly. The size of the crop after a long feeding period does not change in both cases, implying that there is no difference in the termination phase of feeding. There is a possibility that the *Drosophila* link feeding with a familiar source of food and when they experience different food source, they first re-examine it before feeding. Hence, the *hug* neurons seem to regulate feeding initiation based on earlier food encounter.

It has also been shown that starvation of amino acid stimulates yeast feeding by regulating central brain circuits. Two dopaminergic neurons (DA-WED) in each hemisphere of the adult brain innervating the "Wedge" neuropil are suggested to encode protein hunger. The suppression of these neurons results in decrement of yeast intake but elevates the sucrose consumption, whereas if these neurons are triggered they enhances the yeast intake but minimizes the sucrose consumption. Thus, like overall hunger and thirst, nutrient specific hunger motive may also compete for behavioral expression [153].

Mating has also been shown to be responsible for modifying the feeding behavior in female *Drosophila*, and the sex peptide is a key molecule involved in this modulation [154]. Mating improves female's interest in valuable nutrient source (polyamines such as spermine and putrescine). The mated females attract more to the taste and smell of polyamines than virgin females. This modulation in behavior

is regulated through sex peptide receptor (SPR) and its conserved ligands MIPs (myoinhibitory peptides) that directly act on chemosensory neurons [155]. Another modulation in feeding was shown by Walker and colleagues that mating induces a salt appetite in *Drosophila*. Mating promote chances of salt appetite by increasing gustatory response to sodium. It is induced by male-derived Sex Peptide acting on the SPR (Sex peptide receptor) in female reproductive tract neuron [156]. In has been suggested that mating is a pivotal modulator of the decision-making process in female flies and depends on the action of the SPR in internal *ppk+* sensory neurons along with a neuronal TOR /S6K act as an essential input to this decision. The SPR signaling in *ppk+* neurons trigger a robust inclination for yeast in mated females while neuronal TOR/S6K signaling modulates food choices [157].

It has been studied and shown that mushroom body controls the responses of adult flies to learned odours as well as regulates their innate food seeking behavior elicit by food odours. A study depicted that 5 of the 21 types of MBONs (Mushroom body output neurons) are required for starved flies to seek food odours. Four other MBONs (MBON-a3, MBON-b2b02a, MBON-a02 and MBON-g2a01) and their corresponding dopaminergic neurons (DANs) also regulate innate food seeking behavior. Obstructing MBONs and DANs reduce innate food seeking behavior in starved flies, and activation of dopaminergic neurons is sufficient to evoke food seeking behavior in fed flies. The results from RNAi knock-down of different receptors for various hunger and satiety cues illustrates that the MB innervating dopaminergic neurons are modulated by many of these signals, making the MB an integrative center for hunger and satiety signals in the fly brain [158].

11. Influence of taste on food intake and obesity in humans

High calories (especially overconsumption of energy from high fat and sugar foods) and low nutrition density (poor nutrition) are associated with many chronic metabolic diseases including cardiovascular diseases, obesity, diabetes mellitus type 2 and eating disorders in humans. It's a great burden on healthcare system in any country and effective intervention strategies are yet to be found to control them. Past research has suggested that taste impacts the selection of food and its intake in animals as well as other factors like satiation and palatability. Obese and overweight individuals show a tendency of selecting energy-dense-food [159]. In humans, pleasure achieved by food can stimulate "non- homoeostatic" eating making it a prospective player contributing obesity [160]. Nonetheless, factors like previous food experiences, liking, wanting, taste sensitivities and depressed sense of taste cannot be ignored. Many pathways, neural circuits and neurohormones involved as discussed in *Drosophila* section, regulate food intake and decision to stop eating. Internal and external cues also trigger immediate desire to eat specific foods and can impact the final outcome of how much to eat. Similarly, in humans as well several conserved pathways and genes have been observed to play a significant role in controlling feeding behavior.

Although it has been seen that smell also plays a key role in modulating taste perception and influence food intake in individuals [161], but alteration in reward, dopamine signaling, homeostatic signals and affective circuits lead to hedonic eating causing obesity [162, 163]. Various neuroimaging methods have provided insights into central mechanisms underlying taste and hedonic eating highlighting the role of taste circuits in obesity. It has been found food stimuli causes different neural brain responses in obese individuals compared to normal weight people showing striking structural and functional brain circuitry alterations [164–170]. A recent review by [171] and others [172, 173] have beautifully described neural

correlates of sweet, fat, umami, bitter, salty, and sour tastes across brain areas implicated in obesity. Although more conclusive neuroimaging outcomes are required to confirm the role of various taste neural circuits but experimental data indicates different hedonic responses to taste information in obesity. Dysregulations in brain reward circuitry in response to fat and sugar has been associated with obesity [165, 168, 174–177] suggesting fat and sugar affect brain reward circuitry differently. Similarly, high salt consumption has been linked to obesity engaging different brain areas which modulate taste processing and reward [178, 179]. These brain circuits also encode salt taste intensity [178, 180]. Data showing convincing differences in higher salt sensitivities between obese and normal individuals is still insignificant [181, 182]. Studies on neural responses to salt taste in case of obesity are still limited.

Another taste studied in the context of obesity is Umami which contributes to a sense of satiety [183, 184]. Obese individuals show reduced sensitivity but higher preference for umami taste [185, 186] than healthy controls. Since, umami and salt taste both activate primary gustatory cortex circuits in case of umami high tasters compared to low tasters suggest that both tastes share common processing system and may contribute to feeding behaviors implicated in obesity in a similar manner [179]. Bitter taste influence dietary fat consumption suggesting its relevance in obesity [187]. Bitter taste linked with appetite reduction affect many brain areas [188–190]. Conditioning to bitter taste modulates Hedonic evaluation [191]. Alterations in brain activation patters associated with bitter taste in individuals with obesity [190] compared to people without obesity have been observed but more consistent and reliable findings are needed to understand the interaction between brain responses and hedonic ratings of bitter taste [192, 193]. Sour taste is least explored in context of obesity but it plays major role in food selection and consumption and recruit brain regions in sex, age and internal state, condition dependent manner [194, 195]. Neural correlates of sour taste in obesity are limited and require further investigations. dysregulation of gut to brain neural connections and chemosensory pathways along this axis may also contribute to increased risk of obesity [196] suggesting gut could offer potential therapeutic targets in obesity [197]. Nutritional interventions to target neural pathways involved in taste behaviors and perception could offer solutions for prevention and treating obesity in humans.

Further detailed neuroimaging studies to understand taste response, taste physiology and dietary intake in humans and higher animal model systems are required to illustrate the neurobiological underpinnings of taste modalities and their relevance in obesity. Further research to characterize the influence of gut taste receptors and neural circuits on brain responses following food consumption and its modulation by smell in obese individuals that influence food intake are also needed. Collectively, research on invertebrate model system like *Drosophila* shows potential in understanding neurobiological basis of metabolic diseases like obesity at level of neural circuits that regulate feeding behaviors.

12. Conclusion

For the animal fitness, feeding is regulated by peripheral and central feeding circuits to help in acquiring a necessary and balanced dietary input for energy and nutrient homeostasis. It is subjected to intense regulation by multiple neuromodulator systems. In this chapter, we have illustrated recent progress in understanding neural circuits and its modulation in the feeding behavior including local circuits and motor neurons of adult flies which links various internal energy and nutrient

needs to adaptive behaviors. This chapter has integrated information about the structure, function, and molecular regulation of fly taste and feeding circuits. The fruit fly *Drosophila melanogaster*, with many fewer neurons, is ideally suited to understand the complex interactions between neural circuits and genetics that ultimately control behavior. Countless studies have demonstrated the conservation of critical genes between flies and humans, and striking similarities in the organization of the brain, particularly the circuits that process sensory information. A number of functionally distinct populations of neurons in the fly taste circuits have been identified recently in flies that regulate various aspects of feeding behavior. We emphasize on the set or individual neurons that directly or indirectly affects steps in feeding behavior which can be independently adjusted by neuromodulatory cues. How newly identified interneurons that regulate feeding motor program, suppress non- selective ingestion and regulate fluid ingestion connect taste sensory input to the motor output of ingestion as well as interpret top-down information about hunger state is not known. The fruit fly shares the basic metabolic regulation that is conserved throughout evolution. Therefore, simple genetic models like *Drosophila* can provide reliable insights to advance studies in more complex vertebrates, and enhance understanding of specific feeding-related neurological and metabolic disorders in humans. Tracing taste neural circuits in the fly brain, understanding the contribution of taste-independent calorie sensing to feeding, and uncovering novel regulators of neuronal remodeling in the taste system can help elucidate similar principals in higher animals including humans. Together, such studies may provide important clues to how feeding circuits may function in mammals, and lay the groundwork for understanding genetic factors that affect feeding control and body weight.

Humans live in a society very different from the ones that shaped the evolution of our brains. Easy access to cheap, calorie-rich foods has resulted in widespread obesity and an explosion of obesity-related diseases such as type 2 diabetes, hypertension, and heart disease. A detailed understanding of how feeding behaviour is controlled at the level of neural circuits is an important step towards developing new ways to treat and prevent obesity. Humans consume more calories when their diets consist of processed foods [198]. It has been shown that reducing taste sensation at the periphery, a high sugar diet impairs the central Dopamine processing of sensory signals and weakens satiation [199]. Given the importance of sensory changes in initiating this cascade of circuit dysfunction, understanding how diet composition mechanistically affects taste is imperative to understand how the food environment directs feeding behavior and metabolic disease.

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