



Synaptic transmission in Type III taste cells

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ABSTRACT

Background: Type III taste cells are the primary taste receptor cells that form conventional chemical synapses with gustatory nerve fibers. Since the first ultrastructural identification of synaptic vesicles in Type III cells, numerous studies have demonstrated that these cells have synapse-associated proteins and vesicular release machinery that is similar to that in the central nervous system.

Highlight: This review summarizes historical and ultrastructural studies describing synaptic vesicles in taste bud cells across a range of animal species. The classical mechanisms of chemical synaptic transmission in the central nervous system are then outlined, followed by review studies demonstrating the expression of synapse-associated proteins in taste bud cells, with particular emphasis on the putative mechanisms of synaptic transmission in Type III taste cells. Finally, the current evidence for candidate neurotransmitters, including 5-hydroxytryptamine, gamma-aminobutyric acid, noradrenaline, acetylcholine, and ATP, is discussed.

Conclusion: Although several proteins related to conventional chemical synapses in the central nervous system and some candidate neurotransmitters have been identified in Type III cells, their contributions to sour taste transmission have not been fully elucidated. Further molecular and physiological studies are required to establish their roles in the synaptic transmission of sour taste signals from Type III cells.

Abbreviations;

5-HT	5-hydroxytryptamine
GABA	gamma-aminobutyric acid
NA	noradrenaline
ACh	acetylcholine
ATP	adenosine triphosphate
SNARE complex	the soluble N-ethylmaleimide-sensitive fusion attachment protein receptor complex
SNAP25	synaptosome-associated protein 25
SYB2	synaptobrevin 2
STX1	syntaxin 1
CALHM1/3	Calcium homeostasis modulator 1/3
cKO	conditional knockout

1. Introduction

Taste is a chemosensory cue that is crucial for evaluating nutrient intake and avoiding harmful foods in many species. Although the taste modalities are diversified across species, taste is currently classified into

five basic modalities: sweet, umami, bitter, sour, and salty. Taste is not merely utilized as an external stimulus for gustatory evaluation but also serves as a salient signal that modifies internal states such as emotion and appetite, and perception and recognition. In this review, we discuss peripheral sour taste signaling, with a particular focus on vesicular synaptic components relevant to sour signal transmission from Type III taste cell to gustatory nerve fibers.

The peripheral sensory organs for gustation, taste buds, are distributed throughout the tongue, palate and pharynx. Taste buds contain histologically distinct types of taste cells, Type I to IV cells [1–3]. The roles of these cell types are generally considered to be as follows: Type I cells serve as glia-like supportive cells; Type II cells function as sweet, umami, bitter, or amiloride-sensitive salt-responsive cells; Type III cells detect sour compounds; and Type IV cells serve as precursor cells. Thus, Type II and Type III cells are thought to be the primary taste receptor cells.

In sweet, umami and bitter sensitive Type II cells, G protein-coupled receptors (GPCRs), taste 1 receptor member 2/taste 1 receptor member 3 (TAS1R2/TAS1R3), TAS1R1/TAS1R3, and taste 2 receptor members

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(TAS2Rs) detect sweet, umami and bitter compounds, respectively [4]. Ligand binding to these receptors activates an intracellular signaling cascade involving $G\alpha$ gust (Gnat3), phospholipase $C\beta 2$ (PLC $\beta 2$), and transient receptor potential channel M5 (TRPM5), resulting in depolarization followed by the generation of action potentials [5]. In addition, recent studies have demonstrated a TAS1R-independent pathway for sugar detection in the oral cavity [6–8]. Amiloride-sensitive salt taste is also mediated by Type II cells via epithelial Na^+ channel (ENaC). ENaC mediated Na^+ influx causes depolarization and subsequent generation of action potentials [9,10]. These action potentials activate voltage-gated ATP-permeable calcium homeostasis modulator 1/3 (CALHM1/3), leading to adenosine triphosphate (ATP) release from Type II cells. ATP acts as a neurotransmitter by binding to P2X2/P2X3 receptors expressed on gustatory nerve fibers, thereby transmitting taste information to the higher order neurons [11,12]. This type of transmission mechanism is referred to as a "channel synapse" [13].

On the other hand, Type III cells express the H^+ channel OTOPI1, which functions as the sour taste receptor [14,15]. OTOPI1-mediated H^+ influx depolarizes Type III cells, leading to the generation of action potentials. Unlike Type II cells, Type III cells possess the molecular machinery required for conventional vesicular synaptic transmission [2, 3,16,17]. Therefore, signal transmission from Type III cells to the gustatory nerve fibers is thought to be mediated by vesicular synapses. Consistent with this hypothesis, conditional knockout (cKO) mice lacking synaptosome-associated protein 25 (SNAP25) in taste bud cells, a protein essential for vesicular neurotransmitter release, exhibit almost completely loss of chorda tympani (CT) nerve responses to sour tastants [18].

2. Synaptic connections between Type III cells and gustatory nerve fibers

It has long been recognized that synaptic vesicles are present in taste bud cells of the tongue of some animal species and that these cells form synapses with the nerve fibers innervating taste buds. Using electron microscopy, taste bud cells in the rabbit tongue were initially classified histologically into dark cells (Type I cells) and light cells (Type II cells) using electron microscopy [19]. Subsequently, intermediate cells, which exhibit intermediate characteristics between Type I and Type II cells, were identified in rabbit foliate papillae and designated as Type III cells [2]. Type III cells are characterized by the presence of a few dense-cored vesicles and numerous clear synaptic vesicles.

Type III cells are the only taste bud cells that form synaptic contacts with afferent neurons [2]. Thereafter, Type I, II, and III cells have been identified in the taste bud of monkeys, rats, and mice [2,20]. Across these species, Type III cells consistently exhibit a small number of dense-cored vesicles, abundant clear synaptic vesicles, and conventional chemical synapses with nerve fibers [2,3,21]. In mice, some taste bud cells in fungiform, foliate, and circumvallate papillae have synaptic vesicles near the presynaptic membrane and form contacts with nerve fibers, particularly in Type III cells [16,17,20,22,23]. Electron microscopic studies have demonstrated species differences in the distribution of synaptic vesicles among taste cells [2,3,21,23]. Based on these morphological features, these synapse-forming taste cells were long presumed to function as chemosensory receptor cells. With the widespread application of immunohistochemistry, the relationship between the histological classification of Type I–III cells and their gene expression profiles have been established [4,24]. In addition, physiological studies have demonstrated that Type III cells function as sour taste receptor cells and transmit signals to afferent nerves via vesicular synaptic transmission [18,25,26].

3. Molecular mechanisms of synaptic vesicle formation in Type III cells

It has been suggested that synaptic mechanisms in Type III cells are

similar to those operating in the central nervous system. In the central nervous system, synaptic vesicle release is precisely regulated by a variety of proteins at the presynaptic active zone [27,28]. Some of these proteins are also expressed in Type III cells. In this section, we introduce the functions of proteins that have been reported to be expressed in Type III cells, with a particular focus on their established roles in the central nervous system. Although the functions of these proteins in Type III cells have not been fully elucidated, their putative roles are illustrated in Fig. 1.

In the central nervous system, exocytosis of synaptic vesicles is primarily regulated by the soluble N-ethylmaleimide-sensitive fusion attachment protein receptor complex (SNARE complex), which consists of synaptobrevin 2 (SYB2), syntaxin 1 (STX1), and synaptosome-associated protein 25 (SNAP25) [29–31]. STX1 and SNAP25 are located on the plasma membrane and referred to as target membrane-associated SNARE proteins (t-SNAREs), whereas SYB2 is located on the synaptic vesicular membrane and is therefore classified as a vesicular SNARE protein (v-SNARE). An essential accessory component of synaptic vesicular release, synaptotagmin, which is localized to the synaptic vesicle membrane, functions as a Ca^{2+} sensor that triggers the interaction between t-SNARE and v-SNARE proteins, thereby promoting Ca^{2+} -dependent membrane fusion and neurotransmitter release [32,33]. Many other proteins also contribute to the function of chemical synapses. Complexin binds to the SNARE complex and regulates synaptic vesicle fusion by preventing premature membrane fusion while facilitating rapid Ca^{2+} -triggered exocytosis [34,35]. Synaptophysin and synaptogyrin1 are abundant membrane proteins of synaptic vesicles [36]. These proteins participate in synaptic vesicle exocytosis and contribute to synaptic plasticity in the central nervous system [37,38]. Bassoon and Piccolo (PCLO) are major components of the presynaptic active zone cytomatrix, where they help maintain primed synaptic vesicles in a release-ready state [39].

In accordance with the vesicular synaptic release machinery in the central nervous system, the expression of several synaptic proteins has been demonstrated in Type III cells (Table 1). SNAP25 is specifically expressed in rat and mouse Type III cells, as confirmed by immunoelectron microscopy and immunohistochemical analyses [18,40–42]. In contrast, Ueda et al. reported that SNAP25 is expressed in both Type II and Type III cells in rats, which may reflect differences in the antibodies used to recognize the SNAP25a and SNAP25b isoforms [43]. SYB2 is co-expressed with STX1, inositol-1,4,5-triphosphate receptor type 3 (IP $_3$ R3, a marker of Type II cells), and SNAP25 in rat circumvallate papillae, suggesting that it is expressed in both Type II and Type III cells [44,45]. Similarly, STX1 is co-localized with PLC $\beta 2$ and Gnat3 in rat taste buds, indicating its expression in Type II cells [45,46]. However, the expression of SYB2 and STX1 in mouse taste buds has not been demonstrated yet. synaptotagmin 1 is specifically localized in rat Type III cells, as shown by co-immunohistochemistry with Type III cell markers, protein gene product 9.5 (PGP9.5) and neural cell adhesion molecule (NCAM) [47]. Synaptophysin is expressed in both Type II and III cells in rats, as demonstrated by co-immunostaining of SYB2 and PLC $\beta 2$ [48]. Likewise, Synaptogyrin1 is expressed in both Type II and III cells of rat circumvallate papillae [49]. Complexin 2 (CPLX2), which binds to the SNARE complex and regulates synaptic vesicle exocytosis, was first identified as a Type III cell-specific synaptic component in mice [50]. In addition, global *Cplx2* knockout (KO) mice exhibited significant, although incomplete, reduction in CT and glossopharyngeal nerve responses to sour tastants, accompanied by reduced behavioral avoidance to mildly sour stimuli. Transcriptome analysis of mouse taste cells further identified numerous genes related to synaptic transmission and vesicular exocytosis in both Types II and III cells [51]. Sukumaran et al. reported that *Cplx2* and *Pclo* are highly enriched, but not exclusively expressed in Type III cells [51], in contrast to the earlier conclusion by Kurokawa et al. [50]. Bassoon was shown to be specifically expressed in mouse Type III cells [52].

Type III cells have long been proposed to possess conventional

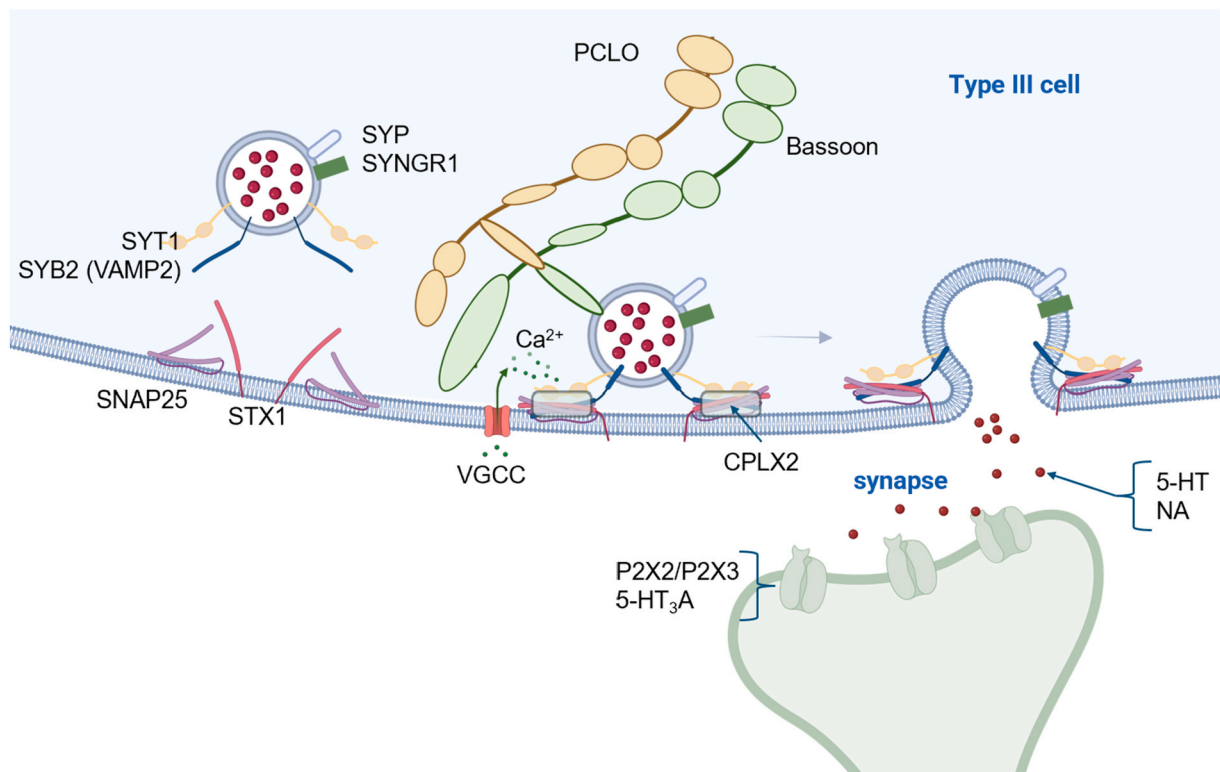


Fig. 1. The schematic diagram of presumed exocytosis of synaptic vesicles in the Type III cell

This schematic model of Type III cells is based on current knowledge of synaptic transmission in the central nervous system. Bassoon and PCLO are believed to contribute to the priming and maintenance of synaptic vesicles in a release-ready state at the presynaptic active zone. CPLX2 regulates the SNARE complex-mediated membrane fusion by preventing premature synaptic vesicle fusion. Upon opening of voltage gated Ca^{2+} channels (VGCCs) during an action potential, the resulting increase in intracellular Ca^{2+} is sensed by STX1. In turn, STX1 triggers SNARE complex-mediated fusion of synaptic vesicles with the plasma membrane and subsequent neurotransmitter release. Moreover, the neurotransmitters and their receptors that are currently known are shown. GABA and ACh are not included in this figure because they are thought to function primarily in cell-to-cell communication within taste buds. Abbreviations: SYP, synaptophysin; SYNGR1, synaptogyrin 1; SYT1, synaptotagmin 1; SYB2, synaptobrevin 2; VAMP2, vesicle-associated membrane protein 2; SNAP25, synaptosome-associated protein 25; STX1, syntaxin 1; VGCC, voltage-gated calcium channel; CPLX2, complexin 2; PCLO, piccolo; GABA, gamma-amino butyric acid; ACh, acetylcholine; 5-HT, 5-hydroxytryptamine; NA, noradrenaline; 5-HT_{3A}, 5-hydroxytryptamine receptor 3A; P2X2/P2X3, purinergic receptors.

chemical synapses based on histological observations. However, the underlying synaptic mechanisms have remained elusive. A recent study provided direct experimental evidence that Type III cells employ SNAP25-mediated synaptic transmission by using epithelial-specific *Snap25* conditional knockout mice (*Keratin5-Cre; Snap25*-floxed, hereafter *Snap25*-cKO mice) [18]. In these mice, CT nerve responses to citric and acetic acid were almost completely abolished. In addition, CT nerve responses to NH_4Cl were significantly reduced, indicating that Type III cells contribute to ammonium taste via SNAP25-mediated synaptic transmission. In contrast, behavioral responses to sour stimuli were unchanged in *Snap25*-cKO mice compared with wild-type mice. This discrepancy between near complete loss of the CT nerve response and the preserved behavioral response to sour tastants may be explained by the contribution of somatosensory acid sensitivity mediated by transient receptor potential V1 (TRPV1) in trigeminal neurons, as behavioral aversive responses to sour stimuli were significantly reduced in *Snap25* and *Trpv1* double KO mice. However, aversive responses to high concentrations of sour stimuli still remained, suggesting the existence of additional acid detection mechanisms in the oral cavity. Interestingly, *Snap25*-cKO mice also showed a reduced number of Type III cells. Although Type III cells were generated normally in *Snap25*-cKO mice, they failed to be maintained in taste buds. These findings suggest that SNAP25 plays an essential role not only in sour taste transmission but also in the maintenance of Type III cells. However, it remains unclear whether other SNARE proteins such as SYB2 and STX1 also contribute to synaptic transmission in Type III cells.

4. Candidate neurotransmitters in Type III cells for signal transmission to gustatory nerves

Taste bud cells contain a variety of neurotransmitters, including 5-hydroxytryptamine (5-HT, serotonin), GABA, noradrenaline (NA), acetylcholine (ACh), and ATP, and some neurotransmitters have been shown to be released from mouse taste bud cells in response to taste stimuli. However, the identity of the neurotransmitter(s) released from Type III cells remains controversial, and discrepancies exist among published studies. Resolving these inconsistencies will require further investigations on neurotransmitter release from Type III cells.

4.1. Serotonin

Serotonin has been localized to Type III cells in taste buds of mice, rats, rabbits and monkeys [53,54]. It was also the first transmitter whose release from mouse taste bud cells was experimentally demonstrated. Using Chinese hamster ovary (CHO) cells expressing 5-HT_{2C} receptors as biosensor cells, serotonin secretion from mouse taste bud cells was demonstrated in response to cycloheximide (bitter), saccharin (sweet) and acetic acids (sour) stimulation [55]. Because biosensors expressing serotonin receptors detect serotonin released from taste cells, and because Type III cells respond to sour stimuli [26] and contain serotonin, it is widely accepted that serotonin is released from Type III cells in response to sour stimulation [56]. Released serotonin is thought to activate gustatory nerve fibers. One candidate serotonin receptor expressed by gustatory nerve fibers is 5-HT_{3A}, as studies using

Table 1

Proteins involved in synaptic vesicles exocytosis.

proteins	cell type	place	species	colocalized proteins	paper
SNAP25	presynaptic taste cells	CV	rat		2000 R. Yang et al.
SNAP25		CV	rat	Gnat3	2000 D W.pumpline et al.
SNAP25	not GPCR-expression cell	CV	mouse	not T1R3/not TRPM5	2006 T R. Clapp et al.
SNAP25	Type II and III	CV	rat	PLC β 2/NCAM	2006 K. Ueda et al.
SNAP25	Type III	CV	mouse	CA4	2025 K. Horie et al.
VAMP2 (Synaptobrevin2)		FuP			
synaptobrevin2		CV	rat	SNAP25	2000 D W.pumpline et al.
VAMP2 (Synaptobrevin2)	Type II and III	CV	rat	SNAP25/5-HT/PGP9.5/IP $_3$ R3	2004 R. Yang et al.
syntaxin	Type II and III	CV	rat	PLC β 2/NCAM	2006 K. Ueda et al.
syntaxin1	Type II and III	CV	rat	PLC β 2/NCAM	2006 K. Ueda et al.
syntaxin1	Type II and III	CV	rat	Gnat3	2000 D W.pumpline et al.
synaptotagmin1	Type III	CV	rat	synaptobrevin2/PGP9.5/5-HT	2007 R. Yang et al.
		CV	rat	PGP9.5/NCAM	2005 R. Kohno et al.
		FuP			
synaptophysin	Type II and III	CV	rat	synaptobrevin2	2009 M. Asano-Miyoshi et al.
synaptogyrin1	T1R2-expressing type II, Type III	CV	rat	T1R2/AADC/NCAM	2013 T. Kotani et al.
complexin2	Type III	CV	mouse	5-HT	2017 S K. Sukumaran et al.
complexin2	Type III	CV	mouse	PKD1L3	2015 A. Kurokawa et al.
		FuP soft palate			
bassoon	Type III	CV	mouse	CA4	2022 R. Ikuta et al.
		FuP			
		FP			
PCLO	Type III	CV	mouse	5-HT	2017 S K. Sukumaran et al.

Abbreviations; CV, circumvallate papillae; FuP, fungiform papillae; FP, foliate papillae; Gnat3, $G\alpha$ gust; T1R3, taste 1 receptor member 3; TRPM5, transient receptor potential channel M5; PLC β 2, phospholipase C β 2; NCAM, neural cell adhesion molecule; CA4, carbonic anhydrase 4; SNAP25, synaptosome-associated protein 25; 5-HT, serotonin; PGP9.5, protein gene product 9.5; IP $_3$ R3, inositol-1,4,5-triphosphate receptor type 3; AADC, aromatic amino acid decarboxylase; PKD1L3, polycystic kidney disease 1-like 3.

5-HT $_3$ A-GFP mice have shown GFP expression in nerve fibers within taste buds and neurons in the geniculate ganglion [57,58]. Pharmacological and genetic evidence further supports this hypothesis. Administration of a 5-HT $_3$ antagonist (ondansetron) to wild-type mice significantly reduced CT nerve responses to NaCl and sour tastants. Similarly, 5-HT $_3$ KO mice exhibit reduced CT nerve responses to various taste stimuli including sour tastants [57]. However, unlike SNAP25-cKO mice [18], 5-HT $_3$ KO mice retain residual CT nerve responses to sour tastants. These findings suggest that additional serotonin receptor subtypes may also contribute to signal transmission from Type III cells to gustatory nerve fibers, although only the 5-HT $_3$ receptor has been identified in taste neurons and nerve fibers [57]. Alternatively, other neurotransmitters may also be candidates for sour signal transmission, as discussed below. Consistent with the proposed role of serotonin as a neurotransmitter in Type III cells, enzymes involved in serotonin synthesis such as tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC) have been identified in Type III cells of mouse, although TPH is also expressed in a subset of gustducin-positive Type II cells [59–61].

4.2. GABA

GABA has been detected in taste bud cells by immunohistochemistry in rats and mice [62–64]. One of the key enzymes involved in GABA synthesis, glutamic acid decarboxylase 67 (GAD67 or GAD1), is specifically expressed in Type III cells [65] whereas GAD65 has been identified in Type I cells [63]. These findings indicate that, at a minimum, Type III cells possess the machinery required for GABA synthesis.

Stimulus-evoked GABA release from mouse Type III cells has been demonstrated using biosensor cells expressing heteromeric GABA $_B$ receptors together with the G-protein α subunit, $G\alpha qo5$ [66]. The potential role of GABA in signal transmission from Type III cells to gustatory nerve fibers was investigated using conditional KO mice lacking GAD67 in taste bud cells [67]. In these mice, expression of GAD67 in Type III cells was completely abolished, suggesting that Type III cells were unable to synthesize GABA. Nevertheless, CT nerve response and behavioral responses to various taste stimuli including sour tastants were largely

comparable between wild-type and GAD67 conditional KO mice. The only detectable difference was a reduction in CT nerve responses to sweet-sour mixtures. These findings suggest that GABA is unlikely to serve as the primary neurotransmitter mediating signal transmission from Type III cells to gustatory nerve fibers, although it may still function as a local modulatory transmitter within the taste bud.

4.3. Noradrenaline

NA has been detected in rat taste bud cells by immunohistochemistry [68]. Stimulus-evoked release of NA from mouse Type III cells has also been demonstrated using biosensor cells expressing $\alpha 1A$ receptors [69]. In contrast, ACh is released from mouse Type II cells in response to a sweet-bitter mixture [70]. These findings suggest that NA, but not ACh, may function as a transmitter in mouse Type III cells. However, the enzymes required for NA synthesis, such as tyrosine hydroxylase (TH) and dopamine β -hydroxylase (DBH), have not been detected in mouse taste buds, although the NA transporter appear to be expressed in Type III cells [60]. This discrepancy raises questions regarding the source of NA in mouse taste buds. The detected NA possibly originates from sympathetic innervation or is taken up via the NA transporter (NAT). In frogs, NA has been reported to enhance gustatory nerve response to various chemical stimuli [71,72]. In addition, DBH-like immunoreactivity has been observed in frog taste organs [73]. These findings suggest that NA functions as a neurotransmitter in the peripheral taste organ of frogs. In contrast, whether NA contributes to signal transmission from Type III cells to gustatory nerve fibers remains unclear since the expression of adrenergic receptors in the taste neurons has not been reported yet.

4.4. ATP

ATP serves as a major energy source for numerous cellular processes, therefore, all taste bud cells are expected to contain abundant intracellular ATP. In rat, purinergic receptors P2X2 and P2X3 are expressed in nerve fibers innervating taste buds [74]. In double KO mice lacking both P2X2 and P2X3, CT and glossopharyngeal nerve responses to taste

stimuli, including sour tastants, are either abolished or markedly reduced compared with those in wild-type mice [12,75]. Likewise, administration of AF-353, a P2X3 antagonist, to wild-type mice significantly reduced CT nerve responses to all taste stimuli [76]. Collectively, these findings demonstrate that ATP plays a crucial role in neurotransmission within the peripheral taste organs. ATP release from Type II cells is mediated by CALHM1/3 [11,77], and does not require vesicular exocytosis. Accordingly, a major part of sweet, umami, bitter and amiloride-sensitive salt taste information is transmitted via CALHM-mediated channel synapses. In contrast, ATP release from Type III cells in response to sour stimuli has not been detected [56,78]. Furthermore, vesicular ATP release requires the vesicular nucleotide transporter (VNUT) for packaging ATP into synaptic vesicles. VNUT has been reported to be expressed in Type II cells but not in Type III cells [79], suggesting that ATP is unlikely to be released from Type III cells via conventional vesicular synapse transmission. Therefore, the marked reduction in sour taste responses observed in P2X2/P2X3 double KO mice cannot be fully explained by ATP release from Type III cells through vesicular synapses alone. Although ATP clearly contributes to sour taste signal transmission, it remains unclear whether ATP is released directly from Type III cells in response to sour stimulation or whether alternative sources or release mechanisms account for the activation of P2X2/P2X3 receptors.

4.5. Acetylcholine

Current evidence suggests that Type III cells are unlikely to employ ACh as a neurotransmitter. Although some taste bud cells express choline-acetyltransferase (ChAT, ACh synthesis) and vesicular ACh transporter (VACHT), the specific cell types of ChAT- or VACHT-expressing cells have not yet been identified [80]. Using biosensor cells expressing M3 muscarinic ACh receptors, researchers demonstrated that Type II cells released ACh in response to taste stimulation [70]. Furthermore, Ca^{2+} -imaging experiments showed that Type III cells respond to ACh, suggesting that they express ACh receptors rather than release ACh themselves [81]. Together, these findings indicate that ACh is more likely to function as an intercellular signaling molecule within taste buds than as a neurotransmitter released from Type III cells.

5. Conclusion

The mechanisms of vesicular synaptic transmission in Type III cells are believed to resemble those operating in the central nervous system and several synapse-associated proteins have been identified in these cells. However, specific functions of those proteins in taste buds remain largely unknown. In addition, the neurotransmitters responsible for signal transmission from Type III cells have yet to be definitively identified. Among the candidate neurotransmitters, ATP is considered the strongest candidate since chorda tympani and glossopharyngeal nerve responses to sour tastants are nearly abolished by genetic deletion or pharmacological inhibition of P2X receptors. However, it has not been demonstrated that Type III cells release ATP in response to sour stimulation or express VNUT required for ATP loading into synaptic vesicles. Therefore, the mechanisms by which ATP could be packaged into synaptic vesicles in Type III cells remains an unresolved question. In contrast, serotonin is released from Type III cells and 5-HT₃ receptors are expressed on the gustatory nerve fibers within taste buds. Nevertheless, inhibition or genetic deletion of 5-HT₃ receptors only partially reduces gustatory nerve responses to sour tastants, indicating that serotonin alone cannot account for synaptic transmission from Type III cells to gustatory nerve fibers. Instead, serotonin may function primarily in intercellular communication within taste buds rather than as the principal neurotransmitter mediating taste bud-to-nerve signaling [82]. Further elucidation of the molecular and cellular mechanisms underlying neurotransmitter release and synaptic transmission from Type III cells will provide important insights into the peripheral coding of sour

taste and advance our understanding of the neural mechanisms of sour taste perception.

Ethical approval

Not applicable.

Author contribution statement

Hinata Tatsukawa: Figures, Writing, Review, Editing. Kengo Horie: Figures, Writing, Review, Editing, Supervision. Ryusuke Yoshida: Figures, Writing, Review, Editing.

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Declaration of competing interest

The authors declare no conflict of interest.

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