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Emerging Role of the Neuronal Sweet Taste Receptor Heterodimer, T1R2+T1R3, in Cognitive Functioning

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ABSTRACT

Diseases involving cognitive impairments present substantial burden to sufferers, families, caregivers and public health. Unfortunately, however, the mechanisms underlying cognitive disorders are yet to be fully unraveled. Taste receptors, initially discovered in the oral cavity, are now believed to be ubiquitously expressed in cells and tissues of the body, including central neurons. Recent investigations have shown that the sweet taste receptor heterodimer, T1R2+T1R3, plays a crucial role in cognitive functioning, suggesting that dysfunctions in sweet taste receptor signaling may underlie cognitive impairment in some brain pathologies. In this mini review, I integrate very recent data that suggest possible molecular mechanisms, linking neuronal sweet taste sensing to cognitive functioning. Future research directions and targeting of sweet taste receptor for potential treatment of brain diseases, involving sweet taste receptor dysfunctions are also discussed.

Key words: T1R2+T1R3, Sweet taste receptors, Neuron, Cognition, Cognitive impairment

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INTRODUCTION

The word "cognition" refers to a variety of subcomponents of higher brain functions such as thinking, reasoning, planning, attention, memory, learning, which are executed by the human brain [1]. However, depending on the context, cognitive functioning can simply refer to learning and memory [2]. Different definitions of cognitive function have been used by other authors [3–11]. Cognitive function is crucial to the effectiveness and ongoing daily life activities of humans [1]. Cognitive disorder or impairment, defined as cognitive decline greater than expected for the person's age and education level, which may interfere with the professional or social life of the sufferer [12], is believed to be the major determinant of disability in late life [1]. Cognitive impairment is a syndrome of several diseases, including Alzheimer's, Parkinson's, and Huntington disease, and multiple sclerosis [12–17]. But Alzheimer's disease accounts for a higher incidence of cognitive impairment: about 60–75% of all cases of cognitive impairment or dementia (severe cognitive impairment) worldwide [18–20]. It should be mentioned that cognitive impairment is a serious problem that can develop even in children and adolescents [21–23]. Depending on the degree of severity, cognitive impairment observed in different neurological diseases poses enormous financial burden to sufferers, families, caregivers and public health [24–28]. Due to the growing prevalence and associated mortality of the neurological diseases, associated with cognitive impairment [24,26], it is evidently necessary to search for new frontiers that will lead to potentially new treatment of cognitive impairment or diseases that predispose to cognitive decline.

Although the mechanisms of development of cognitive decline in different neurological diseases differ, research indicates that neuro- and glio-inflammatory reactions and cell death are critical in almost all diseases associated with cognitive impairment [29,30]. Very recently, emerging data have revealed that dysfunctions of sweet taste receptor signaling may be responsible for cognitive impairment [31], confirming our initial hypothesis about the role of sweet taste receptors in regulation of cognitive functioning [32]. Surprisingly, dysfunctions in sweet taste receptor signaling were also associated with inflammatory response pathway [31]. Zhou et al. recently showed that sweet taste receptors function as pivotal immune sentinels. The authors revealed that key components of the taste signaling cascades (α-gustducin; phospholipase C β2, PLCβ2; monovalent selective cation channel, TRPM5) were down regulated together with abnormal increase in glucose level, which in turn predisposed to elevated intracellular reactive oxygen species, decrease Ca^{2+} and subsequent activation of NLRP3 (NLR Family Pyrin 3) domain containing inflammasome signaling, possibly mediated *via* NF-κB (nuclear factor κB)

activation [31]. Indeed the role of sweet taste receptor signaling in immunity is an important mechanism that link sweet taste receptor with neurodegenerative diseases and glucose metabolism [31]. Emerging data indicate that neuro- and glio-inflammation represents the underlying mechanisms of the etiopathogensis of neurodegenerative diseases [33,34]. Moreover, previous studies have reported not only taste dysfunctions, but also astrocyte-neuron glucose metabolic dysfunctions in neurodegenerative diseases such as multiple sclerosis, Alzheimer's, and Parkinson's diseases [35–41].

Sweet taste receptors are grouped as type 1 (T1R). Functional sweet taste receptors mainly function as dimers and are activated by a plethora of natural and artificial ligands. The natural ligands for sweet taste receptors include monosaccharides (glucose, galactose, fructose), disaccharides (sucrose, maltose, lactose), amino acids (glycine, alanine, threonine, D-histidine, D-tryptophan), and sweet proteins (brazzein, thaumatin, monellin). The artificial ligands for sweet taste receptors include acesulfame potassium, aspartame, cyclamate, sucralose saccharin, glycyrrhizin, and neotame [32]. The second (T2R) type of taste receptors is responsible for sensing bitter substances. This review is concerned only with type 1 taste receptors, in particular, the taste receptor T1R2+T1R3 heterodimer. Taste receptors were initially discovered in the oral cavity, then in other regions of the gastrointestinal tract [42–45], and later in endocrine pancreatic cells [46]. Taste receptors have been found in blood cells, in particular, macrophages [47], and respiratory track [48] and are now known to be ubiquitously expressed in the body. Brain (neuronal) type T1R was fairly recently discovered [49]. Importantly, the authors [49] identified the principal (functional) taste receptor T1R2+T1R3 heterodimer, and all subtypes of sweet taste receptors (T1R1, T1R2 and T1R3) in the neurons of hypothalamus, CA area and dentate gyrus of the hippocampus, and cortex [49]. Interestingly, these brain regions are implicated in both energy homeostasis and cognitive functioning [32]. Indeed discoverers of neuronal sweet taste receptors also showed that these receptors are essential for controlling cerebral metabolism. In a relatively recent review [50], our research group has suggested that T1R2+T1R3 heterodimer is the master coordinator of the astrocyte-neuron metabolic machinery, and highlighted the molecular pathways that link taste sensing with metabolism. Truly, the relationship between glucose metabolism and cognitive functioning has been reported in a couple of studies [51–54]. So, extra-oral sweet taste receptors can mediate a variety of physiological processes, including metabolism, inflammatory responses, and a range of cellular activities [48,55,56].

In light of accumulating evidences, suggesting that sweet taste receptors play an integral role in cognitive functioning and that dysfunctions in components of the signaling pathway of sweet taste receptor may underlie cognitive disorders in some brain pathologies, in this mini review, I integrate very recent studies that suggest possible molecular mechanisms, linking T1R2+T1R3 sweet taste receptor heterodimer sensing in neurons with cognitive functioning. This review also discusses potential research directions that may yield new lines of treatment for brain disorders, involving cognitive impairment such as Alzheimer's disease.

Signal transduction pathway of T1R2+T1R3 receptor heterodimer

The mechanisms of taste receptor signaling involve activation by sweet substance (e.g. glucose), resulting to downstream signaling that culminate in stimulation

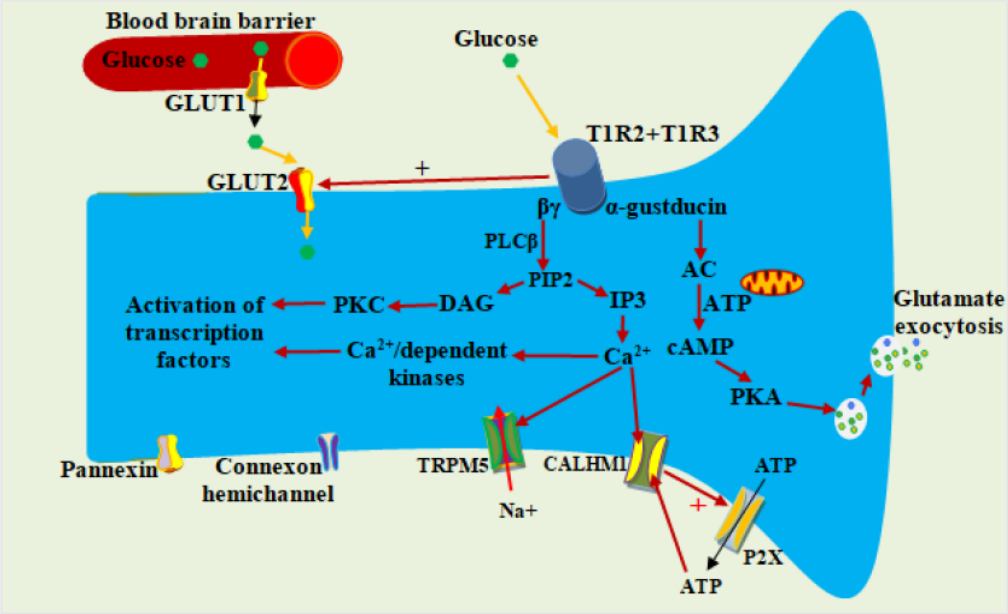

Figure 1: Signal transduction pathway of T1R2+T1R3 receptor

of neuropeptide secretion, activation of transcription factors and gene expression (Figure 1).

In Figure 1, Neuronal T1R2+T1R3 activation by glucose induces intracellular signaling in which the α-subunit gustducin dissociates from the βγ subunits upon exchange of GDP for GTP [57–59]. The α-gustducin activates the membrane bound enzyme adenylate cyclase, which mediates the conversion of ATP to cAMP [60]. However, depending on the isoforms, α-gustducin can also activate phosphodiesterase (PDE) to decrease intracellular cAMP levels [59–61]. Increase in cAMP level can stimulate cAMP-dependent ion channels and protein kinases such as PKA, which when activated, recruits secretory granules towards the plasma membrane for exocytosis. Activated PKA can also translocate to the nucleus to activate gene expression [60]. The βγ subunits activate phospholipase Cβ (PLCβ) with formation of 1,4,5-inositol trisphosphate (IP3). IP3 is responsible for the release of Ca^{2+} from intracellular stores. Increased Ca^{2+} level in the cytosol activates calcium dependent kinases, monovalent selective cation channel (TRPM5), calcium homeostasis modulator 1 (CALHM1) and other receptors [59,61–63]. The evoked increase in Ca^{2+} may also lead to release of ATP *via* dedicated ion channel receptor [64]. The voltage-gated ion channel, CALHM1, has been implicated in taste related ATP release [43]. DAG, released upon βγ subunit activation, can stimulate protein kinase C (PKC), which phosphorylates or activates several intracellular targets, including transcription factors. A couple of secretory neuro-peptides and hormones may be released in T1R2+T1R3 receptor downstream signaling [32]. Events resulting to activation of ion channels can lead to membrane depolarization and subsequent generation of action potential [64]. Taste receptor T1R2+T1R3 also cooperates with the membrane glucosensors (e.g. GLUT2) to control glucose uptake. Gap junctions, hemichannels, and pannexins play a role in homeostasis of ions and other signaling molecules in many physiological processes occurring in the neuron [32].

Deciphering the mechanisms of neuronal T1R2+T1R3 involvement in cognitive functioning

Cognition is a higher mental function of the neocortex, required for almost all activities of humans as well as survival. Cognition depends not only on neocortical, but also hippocampal processes. This higher brain function is also related to several facets of behavior and emotion [32,65]. Based on accumulating data, it is suggested in this paper that T1R2+T1R3 signaling is coupled to neural network of cognition *via* neurotransmitter, cAMP-, Ca^{2+}-dependent and PKC related transcription activation and the expression of early response gene (also known as immediate early genes). Indeed cAMP-, Ca^{2+}-dependent signaling and activity of certain protein kinases (including PKC and PKA) that culminate in activation of transcription of early response genes have been known to underlie memory formation, storage and retrieval. Early response genes are a class of genes that increase transiently in expression in response to extracellular signals such as neurotransmitters. Early response genes code for transcription factors that transiently increase transcription in certain areas of the brain upon stimulation. The transcription factors play a crucial role in signal transduction cascades, necessary for memory formation and consolidation [66]. They form important molecular nexus between neuronal activity and cognition [67].

T1R2+T1R3 signaling is coupled to cognitive network *via* stimulation of neurotransmitter secretion, transcription signaling and early gene responses

From the discussion above, it is evident that cognitive functioning involves interaction of multiple players at different levels: neuromodulators, neurohormones, neurotransmitters, energy substrates (mainly glucose), and transcription factors [68–70]. Transmitter molecules involved in cognitive functioning include but are not limited to acetylcholine, serotonin, dopamine, d-serine, ATP and glutamate [32,68,71]. Recall that ATP and glutamate are crucial neurotransmitters, involved in sweet taste receptor signaling (Figure 1). Therefore, sweet taste signaling, at least *via* ATP and glutamate, can substantially affect cognitive functioning. Emerging research has shown that taste receptors stimulate the secretion of not only ATP and glutamate, but also serotonin and dopamine [72,73]. These transmitter molecules and a range of receptors (including **N**-methyl-D-aspartate, NMDA receptors; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic, AMPA, receptor) [74] mediate the induction of long-term potentiation (LTP), and synaptic plasticity. Importantly, LTP and synaptic plasticity are factors that are essential for storage and retrieval of neural information [32,68]. LTP and synaptic plasticity are associated with activity dependent neuronal signaling and activity of transcription factors, and are important for memory consolidation [59–61,75,76]. For example, stimulation of group I metabotropic glutamate receptors, G_q coupled receptor (mGluR1 and mGluR5) by glutamate can trigger a range of cellular signaling (PLCβ, certain isoforms of adenylate cyclase and MAP kinase) that ultimately result in LTP induction that underlie long-term synaptic plasticity and metaplasticity in neuronal assemblies [68,76,77–79]. Several protein kinases including MAP kinase, CaMKIIα, CaMKβ, PKA and PKC are involved in LTP induction and synaptic plasticity [80]. These protein kinases, in addition to cAMP and calcium ions, can regulate the activities of transcription factors such as enhancer-binding protein (EBP), CREB (cAMP related element binding protein), early growth response protein (egr) (also known as zinc finger protein 225, Zif268; nerve growth factor-induced protein A, NGFI-A), activator protein-1 (AP-1), Rel/NF-κB, Elk-1, c-Jun, Jun-B, Jun-D, c-fos [32,66,81–84] and neuronal PAS domain protein 4 (Npas4) [67], which are implicated in long-term synaptic plasticity and memory consolidation. The signaling of these transcription

factors is largely dependent on neuronal activity [74,83]. It is believed that some of these transcription factors also influence activity-dependent expression of cytoskeleton-associated protein (e.g. activity-regulated cytoskeletal-associated protein, Arc; and cofflin) [85,86] as well as girdin (girders of actin filament) [87] to modulate a range of physiological processes associated with synaptic plasticity and metaplasticity. Interestingly, Ca^{2+}, cAMP, PKA, and MAP kinase activation have been shown to be involved in Arc gene induction [88]. The cytoskeletal protein, Arc, acts as a master regulator of synaptic plasticity and long-term memory formation *via* regulation by MAP kinase phosphorylation [89].

The results of some researchers indicate that late response factors such as brain-derived neurotrophic factor (BDNF) play a pivotal role in LTP induction and synaptic plasticity to influence memory formation, storage and retrieval [90].

Finally, it should mentioned that the expression of memory related genes are dependent on increased recruitment of histone deacetylase 2, an epigenetic enzyme, which forms a repressor complex with zinc finger transcription factor that regulates cognitive functioning [84,91,92]. The role of epigenetic enzymes in cognitive functioning has been reviewed elsewhere [93–97].

Cognitive processes are coupled to cerebral glucose metabolism by the T1R2+T1R3 receptor heterodimer

From Figure 2, it is obvious that T1R2+T1R3 signaling is coupled to cognitive processes *via* glucose metabolism.

In addition to the signaling pathway triggered upon activation of taste receptor heterodimer as defined in Figure 1, T1R2+T1R3 can stimulate the functions of GLUT2 to increase glucose uptake. Increase in glucose uptake is associated with cerebral insulin signaling [32]. (Cerebral insulin can signal downstream to regulate the activities of early genes or SIRT1) [98,99]. Glucose, a crucial energy molecule, in the cytosol undergoes several metabolic reactions to produce ATP and other substances required for physiological processes in neurons. Increased level of cellular ATP promotes inhibition of potassium fluxes by the K-ATP channel. The level of ATP in the cell is constantly been monitored by energy sensors, in particularly, AMPK, which also interacts with SIRT1 to regulate the activities of early genes and the epigenome. Again, under the action of adenylate cyclase, ATP can be converted to cAMP, which in turn activates PKA. The activated PKA can interact with several effectors: It activates secretory granule exocytosis and transcription factors (Neuron A) [32,98,99]. The exocytosed molecules (e.g. neurohormones) diffuse to neighboring neurons to

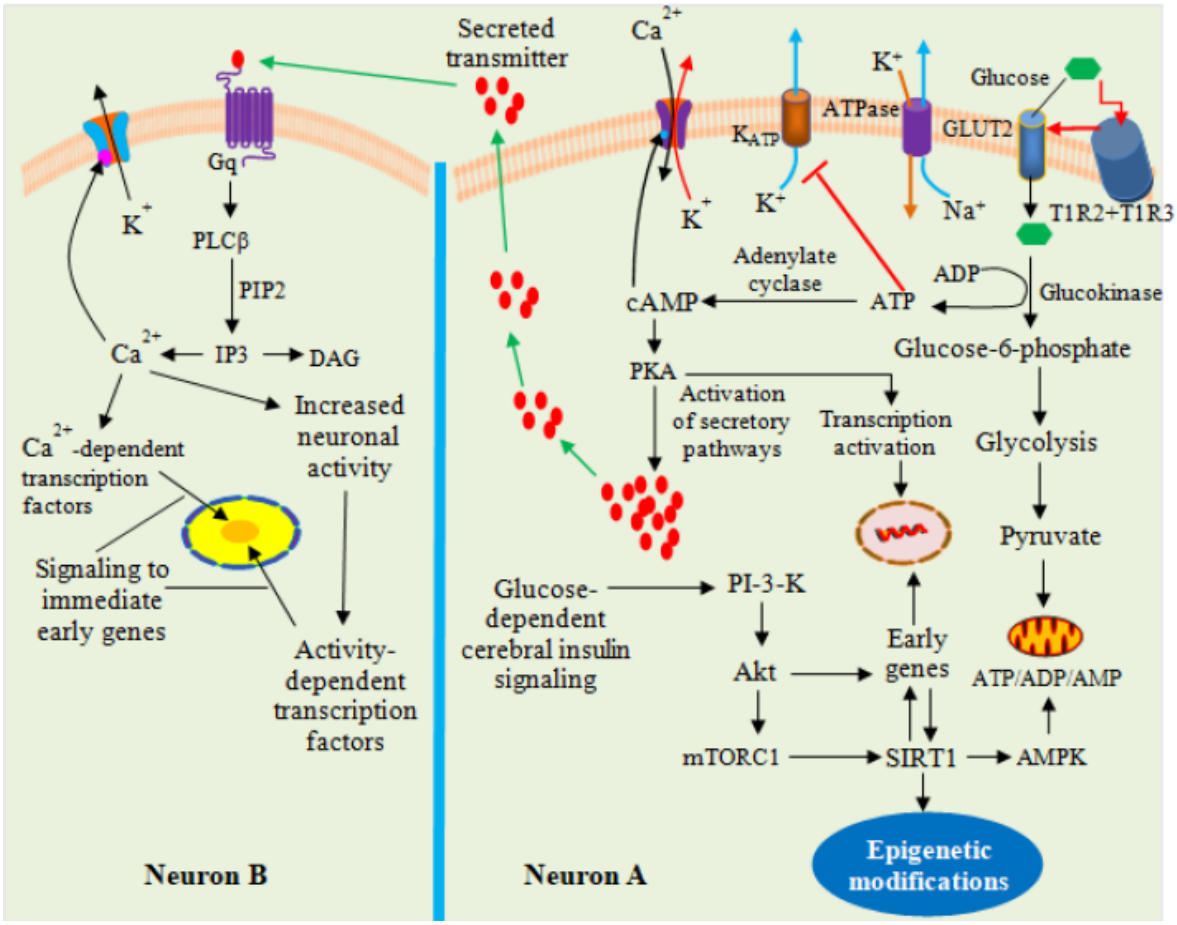

Figure 2: Mechanisms of coupling of T1R2+T1R3 signaling to cognitive network of the brain

stimulate their cognate receptors, which trigger a series of cascades, culminating in increased cytosolic calcium, and subsequently, activation of certain membrane receptors, transcription factors, and the expression of early response genes that are involved in synaptic plasticity, memory and learning (Neuron B) [32].

The relationship between glucose metabolism and cognitive processes has been demonstrated in a couple of studies [51,100,101]. This functional cross-talk is possible due to the interaction between metabolic products of glucose and cognitive circuitry [102]. Metabolic signals have been shown to determine reward or emotion [103–106] from sugar ingestion. A recent study by Chan et al. [107] revealed that stimulation of sweet taste receptors by ingestion of non-nutritive, non-calorie sweeteners stimulated glucose transport, incretin effect and insulin secretion. The result was enhancement of glucose metabolism. Similar results were reported by Murovets et al. [108], who showed an association between T1R3 defect and disorder of glucose transport in mice. Furthermore, it was shown that activation of brain sweet taste receptors was associated with incretin effect.

The different substances produced from glucose *via* series of metabolic processes–glycolysis and oxidative phosphorylations are involved in maintenance of cognitive systems [109]. Accumulating data have shown that metabolic coupling to cognition is believed to occur *via* lactate synthesis [65,80,110,111]. Neuronal metabolism, culminating in lactate production, is involved in LTP induction, synaptic plasticity, memory formation, which are thought to involve the activation of CREB, Arc and cofilin [112]. Relatively recent animal study demonstrated that defect in lactate transport is associated with disorder in memory formation [112]. Though lactate itself may not directly enhance cognition, its metabolic products in the TCA cycle and their activation of transcription factors may be necessary for lactate enhancement of cognitive functions [112]. Neuron-derived lactate appears to stimulate the expression of genes (Arc, c-Fos, and Zif268), which are associated with synaptic plasticity [113]. Indeed lactate may serve as substrate for the synthesis of synaptic or structural proteins such as Arc and cofflin, which may occur *via* transcription regulation [80]. In this regard, previous data have consistently shown that AMPK, CREB and mTOR are involved in both glucose metabolism and memory functions [71]. Importantly, these molecules are strongly involved in T1R2+T1R3 signaling [32]. Furthermore, Yang et al. [113] reported that infusion of lactate resulted to potentiation of NMDA receptor activity, which is involved in LTP induction and memory formation. Data have consistently shown that AMPK and other metabolic sensors are involved in both glucose metabolism and cognitive functions [114]. Thus disorders involving metabolic sensors such as AMPK and mTOR can result to cognitive decline, and more importantly, have been associated with neuropsychiatric symptoms, including intellectual disability, specific neuropsychological deficits, and other behavioral and cognitive disorders [115].

CONCLUSION

The T1R2+T1R3 heterodimer is a functional sweet taste receptor that drives cerebral glucose metabolism and regulates cognitive functioning. The possible molecular mechanisms, linking neuronal sweet taste sensing to cognitive functioning involves multiple cross-talks with membrane glucosensors (GLUT2, K_{ATP}), cytosolic glucosensors and epigenetic factors (SIRT1, AMPK and mTOR), and transcription factors (EBP, CREB, egr, AP-1, Rel/NF-κB, Elk-1, c-Jun, Jun-B, Jun-D, c-fos, Npas4), and other signaling molecules: Ca^{2+}, cAMP, protein kinases (PKA, PKC, MAP kinase). Activity dependent signaling by neuronal T1R2+T1R3 is critical for both metabolic and cognitive processes in health and disease.

FUTURE DIRECTIONS

Since T1R2+T1R3 heterodimer signaling is related to cognitive functioning (Figure 2) [31,32], future research will investigate the effects of downstream signaling of neuronal sweet taste receptors on cerebral and global glucose homeostasis in health and disease. Specific attention will be given to diabetes mellitus, prediabetes, and brain diseases involving both cognitive decline and metabolic dysregulation (e.g. neurodegenerative disorders–Alzheimer, Parkinson diseases etc.). Further investigations into the effects of different pharmacological agents on sweet taste receptor functions can yield potential treatment options for brain diseases, involving both metabolic and cognitive dysregulation.

CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this paper.

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