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Review

Modulation of sweet responses of taste receptor cells

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ABSTRACT

Taste receptor cells play a major role in detection of chemical compounds in the oral cavity. Information derived from taste receptor cells, such as sweet, bitter, salty, sour and umami is important for evaluating the quality of food components. Among five basic taste qualities, sweet taste is very attractive for animals and influences food intake. Recent studies have demonstrated that sweet taste sensitivity in taste receptor cells would be affected by leptin and endocannabinoids. Leptin is an anorexigenic mediator that reduces food intake by acting on leptin receptor Ob-Rb in the hypothalamus. Endocannabinoids such as anandamide [N-arachidonoylethanolamine (AEA)] and 2-arachidonoyl glycerol (2-AG) are known as orexigenic mediators that act via cannabinoid receptor 1 (CB_1) in the hypothalamus and limbic forebrain to induce appetite and stimulate food intake. At the peripheral gustatory organs, leptin selectively suppresses and endocannabinoids selectively enhance sweet taste sensitivity via Ob-Rb and CB_1 expressed in sweet sensitive taste cells. Thus leptin and endocannabinoids not only regulate food intake via central nervous systems but also modulate palatability of foods by altering peripheral sweet taste responses. Such reciprocal modulation of leptin and endocannabinoids on peripheral sweet sensitivity may play an important role in regulating energy homeostasis.

Contents

Abbreviations: 2-AG, 2-arachidonoyl glycerol; AEA, anandamide (N-arachidonoylethanolamine); BMI, body mass index; CB_1 (or CB_2), cannabinoid receptor 1 (or 2); CT, chorda tympani; CTA, conditioned taste aversion; GAD67, glutamate decarboxylase 67; GL, glossopharyngeal; i.p., intraperitoneal; IP_3R3, inositol 1,4,5-trisphosphate receptor type 3; IRS, insulin receptor substrate; JAK, Janus kinase; K_{ATP} channel, ATP-sensitive K^+ channel; KO, knock-out; PI3K, phosphoinositide-3-kinase; PLCβ2, phospholipase C β2; RT-PCR, reverse transcriptase polymerase chain reaction; SGLT1, Na^+/glucose cotransporter 1; STATs, signaling transducers and activators of transcription; T1R2 (or T1R3), taste receptor family 1 member 2 (or 3); TRPM5, transient receptor potential cation channel subfamily M member 5; VGSC, voltage gated sodium channel.

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1. Introduction

To evaluate the quality of food components, animals use the gustatory system. Heretofore, sweet, umami, bitter, salty and sour tastes are generally accepted as basic tastes in humans. Among them, sweet taste is elicited by sugars, artificial sweeteners (such as saccharin, aspartame, cyclamate, and acesulfame K), sweet amino acids and sweet proteins (such as brazzein, thaumatin, curcurin, and miraculin) and is very attractive for humans and some animals because sweet taste indicates the existence of carbohydrate sources of calories in foodstuffs. Recent studies have revealed molecular mechanisms for reception and transduction of sweet taste. G-protein coupled receptors, taste receptor type 1, member 2 (T1R2) and member 3 (T1R3), form heterodimers to act as sweet taste receptors [1,2]. Sweet tastant binding to T1R2 + T1R3 activates the following signaling cascade comprised of heteromeric G-protein (including Gα-gustducin), phospholipase C β2 (PLCβ2), inositol-1,4,5-triophosphate receptor type 3 (IP_3R3), and transient receptor potential channel M5 (TRPM5) [3–5]. Finally, taste cells are depolarized, generate action potentials, and release transmitters (ATP) via pannexin-1 hemichannels [6–8]. Released ATP would activate adjacent gustatory nerve fibers expressing purinergic receptor P2X2 + P2X3 [9], then sweet information is send to the higher order neurons [10].

Sweet taste sensitivity might not be constant but would be affected by some internal and external factors. For example, the perceived sweetness of diluted sugar solutions increases strongly with temperature [11,12]. This would be explained by the nature of a sweet transduction component TRPM5, which is a highly temperature-sensitive, heat-activated channel. Activation of this channel by temperature peaking at 35 °C near body temperature, leads to an increase of the sweet sensitivity of the taste cell [13]. As internal factors affecting sweet taste sensitivity, leptin and endocannabinoids are reported to modulate peripheral taste sensitivity via their cognitive receptors, Ob-Rb and cannabinoid receptor 1 (CB_1), respectively [14,15]. Leptin, an anorexigenic mediator that reduces food intake by acting on hypothalamic receptors [16], selectively suppresses sweet taste responses. In contrast, endocannabinoids, orexigenic mediators that induce appetite and stimulate food intake via hypothalamic receptors [17], selectively enhance sweet taste responses. Thus, leptin and endocannabinoids not only regulate food intake via central nervous systems but also modulate palatability of foods by altering peripheral sweet taste sensitivity. In this review, we will focus on the effect of leptin and endocannabinoids on peripheral sweet taste sensitivity.

2. Effect of leptin

2.1. Leptin, leptin receptors, and their mutant (ob/ob and db/db) mice

The hormone leptin is the product of the obese gene (*ob*) and is primarily produced by adipocytes. Leptin regulates food intake, energy expenditure, and body weight. The mutant mice having a defect in the *ob* gene (*ob*/*ob* mice), which prevents leptin production, exhibit severe obesity, hyperphagia and diabetes [18]. Leptin acts by binding to a specific obese receptor (Ob-R) encoded by the *db* gene. There are five isoforms (Ob-Ra-e), which are generated as splice valiants of the *db* gene. The mutant mice having a point mutation of the *db* gene (*db*/*db* mice) lack the functional leptin receptor (Ob-Rb), thus these mice are also hyperphagic, massively obese, and diabetic [19]. Ob-Rb is abundantly expressed in several hypothalamic nuclei, which are major target sites for leptin. However, Ob-Rb is also expressed in peripheral organs, such as lymph nodes, liver, lung, uterus, adipose tissue, kidney and pancreas [20]. We have demonstrated that taste organ is additional peripheral target of leptin.

Possible effect of the *db* gene on taste sensitivities was examined by comparing chorda tympani (CT) nerve responses between *db*/*db* and lean control mice [21–25]. The CT nerve innervates taste buds in the anterior part of the tongue (fungiform papillae and the anterior part of foliate papillae). The *db*/*db* mice showed greater CT nerve responses to sweet compounds including sugars and artificial sweeteners than lean control mice. CT nerve responses to other basic taste compounds such as NaCl, HCl and quinine were not significantly different between *db*/*db* and lean control mice. Such greater CT nerve responses to sweet compounds were also observed in *db*/*db* mice at 7–9 days of age but not in streptozotocin-induced adult diabetic mice [23], indicating that the diabetic status itself might not be essential for the greater CT nerve responses to sweeteners. In behavioral study assessed by two-bottle preference test, taste preference scores for sucrose, fructose, glucose and maltose were generally higher in *db*/*db* mice than in lean control mice [23]. Thus, sweet taste sensitivities are likely to be regulated by the *db* gene product. In 1994, the *ob* gene was cloned and found to encode the protein leptin [18]. Soon after this discovery, the *db* gene was cloned and found to encode Ob-R and the *db*/*db* mouse mutation occurs at the intracellular domain of Ob-R [19]. These findings leaded to investigation of the effect of leptin on sweet taste sensitivities in mice.

2.2. Sweet suppressive effect of leptin in mice

To examine the effect of leptin on taste sensitivities, CT nerve responses to various taste stimuli before and after intraperitoneal (i.p.) injection of recombinant leptin were compared in both *db*/*db* and lean control mice [14]. In control mice, CT nerve responses to sucrose and saccharin started to decrease about 10 min after the injection of leptin (100 ng/g body weight) and reached maximal inhibition levels (65% of control) about 30 min after the injection. Plasma leptin level increased to about 6.0 ng/ml from the basal level (approximately 3.5 ng/ml) at 10 min after the injection and reached about 12.0 ng/ml at 30 min. CT nerve responses to sweet substances were significantly suppressed but those to other taste substances (NaCl, HCl and quinine) were not reduced after leptin administration, suggesting that leptin selectively suppresses sweet taste sensitivity. Such suppression was not observed in *db*/*db* mice even though higher dose of leptin (500 ng/g body weight) was administrated and plasma leptin level was elevated from 90 to above 150 ng/ml. In control mice, sweet suppressive effect of leptin was also observed in the glossopharyngeal (GL) nerve innervating the posterior part of the tongue (circumvallate papillae and the posterior part of foliate papillae). In addition, the strength of suppressive effects by leptin was at most about 30% of control responses, and the effect may saturate when plasma leptin concentration reaches about 15–20 ng/ml [14,26].

Leptin also affected behavioral responses to sweet compounds. Using a conditioned taste aversion (CTA) paradigm and sweet–bitter mixture paradigm, changes in short time (10 s) lick responses to taste compounds before and after i.p. injection of leptin were analyzed in *db*/*db*, *ob*/*ob* and lean control mice [27,28]. In CTA paradigm, lean mice were conditioned to avoid 0.1 M sucrose solution by i.p. injection of LiCl after drinking the conditioned stimuli (sucrose). These conditioned mice avoided to lick sucrose solutions. Lick responses of conditioned mice to 0.03–0.05 M sucrose were significantly increased 10–60 min after i.p. injection of leptin (100 ng/g body weight), whereas conditioned mice administrated with same volume of saline did not show such increases in lick responses to sucrose solutions. In sweet–bitter mixture paradigm, *db*/*db*, *ob*/*ob* and lean control mice showed concentration-dependent lick responses to sucrose and saccharin.

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When these mice were administrated with leptin, *ob*/*ob* and lean control mice showed decreased lick responses to sucrose and saccharin but *db*/*db* mice did not. Lick responses to other tastants were not affected by i.p. injection of leptin in all types of mice. Thus, leptin affects selectively perceived sweet taste sensitivity of mice.

The target of leptin to elicit the sweet suppressive effect would be taste receptor cells. Reverse transcriptase polymerase chain reaction (RT-PCR), in situ hybridization and immunohistochemical analyses demonstrated that functional leptin receptor Ob-Rb was expressed in the fungiform and circumvallate taste bud cells [14,28–30]. In both fungiform and circumvallate taste buds, about 30–40% of T1R3 expressing cells coexpressed Ob-Rb (Jyotaki et al., unpublished observation), indicating that a subset of sweet sensitive cells would possess functional leptin receptors. It was also found that potassium outward currents of isolated taste cells in response to depolarizing voltage steps were increased during bath application of leptin [14]. Increase of potassium outward current may lead to reduction of cell excitability. Indeed, we have recently found that about a half of sweet-responsive cells showed significant reduction of impulse frequencies in response to sweet stimuli during the bath application of 10–20 ng/ml leptin (Fig. 1A) [31–34]. Thus, leptin suppresses sweet taste sensitivity in mice by affecting responsiveness of sweet sensitive (maybe T1R3-expressing) taste cells via Ob-Rb.

2.3. Leptin and sweet taste in humans

Leptin may also influence human sweet taste sensitivities. Plasma leptin levels show a diurnal variation in both rats and humans [35,36]. In humans, leptin levels start rising before noon and peak between 23:00 h and 01:00 h, after which the levels decline until morning [37]. This diurnal variation of leptin levels exhibits meal-related shifts. When meals were shifted by 6.5 h without changing the light or sleep cycles in humans, the plasma leptin levels were similarly shifted by 5–7 h [38]. The nocturnal rise of leptin does not occur if the subjects are fasted [39]. Therefore, if leptin also affects human sweet taste sensitivity, and it shows diurnal variation, then it follows that the threshold for sweet taste may show correlated diurnal variation. This possibility was tested with non-obese human subjects with body mass index (BMI) < 25 [40].

Recognition thresholds for various taste stimuli, plasma leptin levels, blood glucose levels and plasma insulin levels were measured at seven time points (8:00, 9:30, 12:00, 14:00, 17:00, 19:00 and 22:00) during the day under normal meal conditions with three meals (8:30, 12:30 and 17:30), and restricted meal conditions with one (17:30) or two meals (12:30 and 17:30) per day. In the normal feeding condition, plasma leptin levels started rising before noon and peaked in the night. At the same time, significant time-dependent increases in recognition thresholds for sucrose, glucose, and saccharin were observed in the normal meal condition. That is, subjects required higher concentrations of these sweeteners to detect the stimulus quality when they were tested in the evening compared to the morning. In the two and one meal condition, the rise in leptin levels occurred later resulting in a phase shift of diurnal variation. There was also a phase shift in the two or one meal conditions eliminating the time dependent changes in recognition thresholds for sweeteners. Diurnal variations in recognition thresholds for sweeteners were significantly different among 3 meal conditions. This diurnal variation is sweet taste specific; recognition thresholds for NaCl, citric acid, quinine and monosodium glutamate did not exhibit such diurnal variations. Thus, plasma leptin levels may specifically affect sweet taste sensitivity in healthy non-obese human subjects. In contrast, the significant diurnal variations for sweet recognition thresholds were

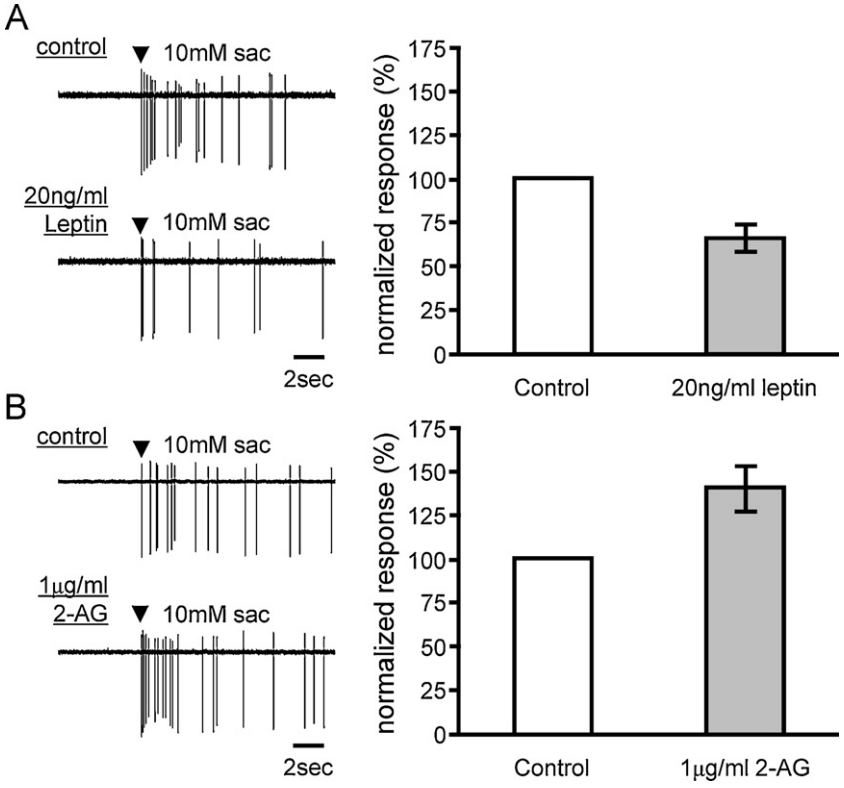

Fig. 1. Effects of leptin (A) and 2-AG (B) on taste responses of sweet sensitive taste cells in mouse fungiform taste buds. Left: A sample recording showing the effect of bath application of 20 ng/ml leptin (A) or 1 μg/ml 2-AG (B) on responses of a taste cell to 10 mM saccharin (sac). These recordings were obtained from different taste cells. Right: Summarized effect of 20 ng/ml leptin (A, $n = 19$, $P < 0.01$, t-test) or 1 μg/ml 2-AG (B, $n = 19$, $P < 0.01$, t-test) on sweet taste responses of taste cells.

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not observed in the overweight and obese subjects (BMI > 25, Sanematsu et al. unpublished observation). Mean plasma leptin levels (at 8:00) of the overweight and obese subjects are about 20 ng/ml, which are close to the saturation level of leptin effect in mice (about 15–20 ng/ml) [14]. This suggests that no significant diurnal variations for sweet recognition thresholds in the over-weight and obese subjects may be due to their higher basal plasma leptin levels.

2.4. Possible signaling pathway activated by leptin

As mentioned before, leptin may suppress responses of sweet sensitive taste cells by increasing potassium outward currents. However, intracellular signaling pathway mediating sweet suppressing effect of leptin is still unclear. Leptin binding to Ob-Rb is known to activate various intracellular signaling pathways [41]. One of main signaling cascades is mediated by Janus kinases (JAKs) and signaling transducers and activators of transcription (STATs). Indeed, taste bud cells express STAT3, which would transduce leptin signal [29]. Activation of JAKs also recruits various downstream signaling molecules such as insulin receptor substrate proteins and phosphoinositide-3-kinase (PI3K). Among them, activation of PI3K may be a key for increases in potassium currents. Some neurons in the hypothalamus, the dorsal motor nucleus of the vagus and the nucleus of the solitary tract are hyperpolarized by leptin [42–44]. These effects are mediated by activation of ATP-sensitive K^+ (K_{ATP}) channel. Inhibitor of PI3K prevents activation of K_{ATP} channel by leptin, implicating PI3K in leptin receptor coupling to K_{ATP} channel. Recently K_{ATP} channel is reported to present in T1R3-expressing taste cells [45]. Therefore in a manner similar to these neurons, sweet sensitive cells may be hyperpolarized by leptin via PI3K-driven activation of K_{ATP} channel (Fig. 2). Large conductance Ca^{2+} activated K^+ channels may be another target for leptin because leptin inhibits hippocampal neurons via PI3K-driven activation of this channel [46].

3. Effect of endocannabinoids

3.1. Why endocannabinoids?

Returning to the taste sensitivity of mice, leptin selectively suppresses sweet taste responses in wild-type mice but not in *db*/*db* mice. This may be one major reason for greater responses to sweeteners in *db*/*db* mice. However, disinhibition of leptin effect may not fully account for the greater sweet responses in *db*/*db* mice. We hypothesized that some hormones or bioactive substances that have an inverse effect of leptin might enhance sweet taste sensitivity. In 2001, it was reported that defective leptin signaling is associated with elevated hypothalamic levels of endocannabinoids in *db*/*db* and *ob*/*ob* mice and Zucker rats [47]. Endocannabinoids, such as anandamide [N-arachidonoylethanolamine (AEA)] and 2-arachidonoyl glycerol (2-AG), are known as orexigenic mediators that act via CB_1 in the hypothalamus and limbic forebrain to induce appetite and stimulate food intake [17,48,49]. Furthermore, acute leptin treatment of normal rats and *ob*/*ob* mice reduces AEA and 2-AG in the hypothalamus. CB_1 antagonist SR141716 reduces food intake in wild-type mice but not in CB_1-knockout (KO) mice [50]. These findings indicate that endocannabinoids in the hypothalamus appear to be under negative control by leptin and contribute to overeating in the development of obesity. If this is also the case in peripheral taste system, it is possible that greater sweet taste responses in *db*/*db* mice might be due not only to lack of inhibitory effect of leptin but also to the effect of endocannabinoids. Therefore, the effect of endocannabinoids on peripheral taste sensitivities in mice was examined [15].

3.2. Sweet enhancing effect of endocannabinoids in mice

We first recorded CT and GL nerve responses of the wild-type mice to various taste stimuli before and after i.p. injection of AEA or 2-AG. The administration of AEA or 2-AG in wild-type

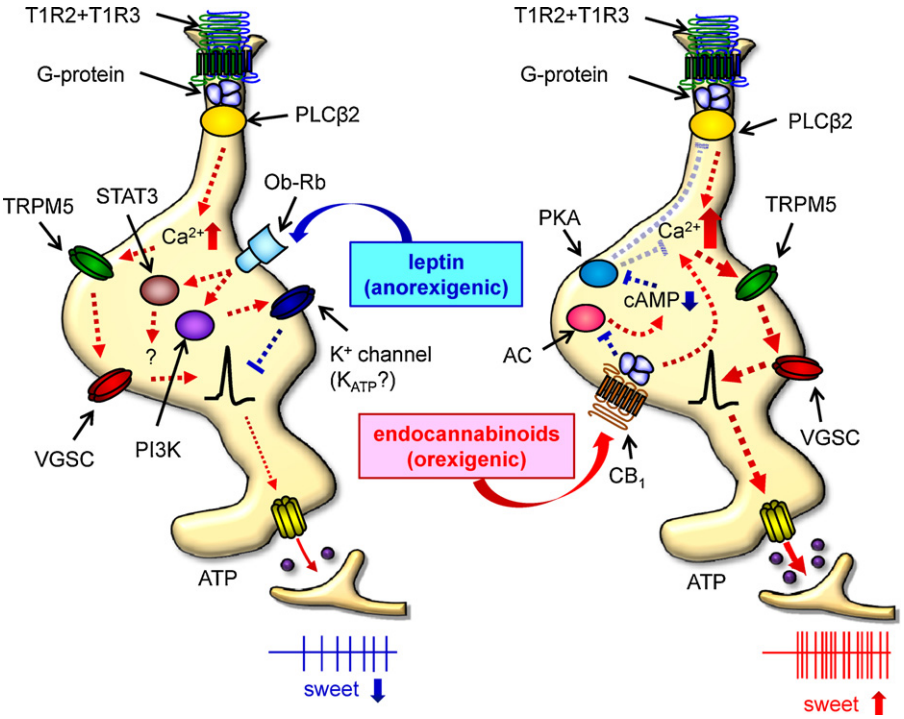

Fig. 2. Possible intracellular signaling pathways mediating the effects of leptin (shown in left) and endocannabinoids (shown in right) on sweet sensitivities of taste cells. For more detailed information, see the text. VGSC: voltage gated sodium channel; PKA: protein kinase A; AC: adenylyl cyclase.

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mice increased CT and GL nerve responses to sweeteners (sucrose, saccharin, glucose and SC45647) in a concentration-dependent manner (0.01–1 μg/g body weight), whereas no such increase was observed in responses to salty (NaCl), sour (HCl), bitter (quinine) and umami (monosodium L-glutamate) compounds. After i.p. injection of AEA or 2-AG, increased responses to sweet compounds (~150% of control for 500 mM sucrose) were observed at 10–30 min postinjection and then recovered to the control level at 60–120 min postinjection. Consistently, both AEA and 2-AG selectively enhanced behavioral lick responses to sucrose-quinine mixtures, whereas no such effect was observed in lick responses to salty, sour, bitter and umami compounds. Enhancing effect of 2-AG and AEA on gustatory nerve responses and behavioral responses to sweeteners was not observed in CB_1-KO mice, indicating that this effect is mediated by CB_1.

We next examined the effect of endocannabinoids on taste cell responses to sweeteners. In about 60% of sweet sensitive taste cells, basolateral administration of 1 μg/ml 2-AG or AEA increased (>120%) responses to sweeteners (Fig. 1B), suggesting that endocannabinoids directly modulate taste responses of sweet sensitive taste cells. Similar to neural and behavioral responses, sweet responses of taste cells in CB_1-KO mice were not affected by 1 μg/ml AEA or 2-AG. Moreover, an antagonist for CB_1 receptor AM251, but not for CB_2 receptor AM630, suppressed the sweet enhancing effect of 1 μg/ml 2-AG. RT-PCR study demonstrated that mRNAs for CB_1 were expressed in both fungiform and circumvallate taste buds. In addition, immunohistochemical study demonstrated that about 60% of taste cells expressing T1R3 in both fungiform and circumvallate taste buds also expressed CB_1. In CB_1-KO mice, CB_1 immunoreactivity in taste cells was absent. These findings indicate that endocannabinoids elicit their sweet enhancing effect via CB_1 in sweet sensitive taste cells. In the central nervous system, CB_1 are expressed in presynaptic cells and underlie inhibition of transmitter release from presynaptic cells [51]. In the peripheral taste organ, CB_1 was rarely expressed in glutamic acid decarboxylase (GAD67)-expressing taste cells which are thought to be presynaptic cells in mice [52]. GAD67-expressing presynaptic cells are primarily sensitive to sour taste stimuli [53,54], but endocannabinoids did not affect neural and behavioral responses to sour stimuli, indicating that presynaptic cells are not the major target for endocannabinoids in the taste organ. Instead, the majority of taste cells expressing CB_1 are sweet-sensitive cells expressing T1R3, indicating that endocannabinoids act to enhance sweet taste responses through these taste receptor cells known to lack well-elaborated synapses.

3.3. Possible signaling pathway activated by endocannabinoids

Signaling pathway for the enhancement of sweet responses by endocannabinoids is currently unknown. CB_1 is a G-protein coupled receptor and is known to activate several intracellular transduction pathways [55]. The major mediators of CB_1 are the G proteins of Gi/o family, which inhibit adenylyl cyclase activity and cAMP accumulation [56]. Similar to the mechanism proposed in bitter sensitive taste cells, reduction of cAMP level in sweet sensitive cells may suppress activity of protein kinase A leading to disinhibition of the Ca^{2+} signaling effectors PLCβ2 and IP_3R3 [57]. Consequently, endocannabinoids may enhance Ca^{2+} responses of sweet sensitive cells evoked by sweet taste stimuli (Fig. 2). The other possible pathway may be mediated by G-proteins of Gq/11 family or Gβγ subunits which induce elevation of $[Ca^{2+}]_i$. This elevation $[Ca^{2+}]_i$ is synergistically enhanced by sequential activation of CB_1 and other Gi/o coupling receptors, such as M3 muscarinic and δ-opioid receptor, in neuroblastoma cells [58]. This synergistic elevation of $[Ca^{2+}]_i$ does not require activation of voltage-sensitive calcium channels, which may not be expressed in sweet sensitive taste cells [59]. It is possible that sequential activation of CB_1 and sweet taste receptors in taste cells may produce synergistic elevation of $[Ca^{2+}]_i$, which may lead to increase of frequency of action potentials and ATP release for taste signal transmission from the receptor cells to the taste nerve (Fig. 2).

4. Effect of antagonists for Ob-Rb and CB_1

Recently, we have tested whether antagonists for leptin and endocannabinoids affect gustatory nerve responses to various tastants in lean control and *db*/*db* mice (Niki et al., unpublished observation). We used leptin mutant L39A/D40A/F41A as leptin receptor antagonist and AM251 as CB_1 antagonist, respectively. Administration of leptin mutant L39A/D40A/F41A alone (1 μg/g body weight) significantly increases CT nerve responses of lean control mice to sweeteners but not to other tastants such as NaCl, HCl, quinine and monosodium glutamate, whereas administration of AM251 alone (3 μg/g body weight) does not affect CT nerve responses of lean control mice to various tastants tested. In contrast, CT nerve responses in *db*/*db* mice to sweeteners are significantly suppressed by i.p. injection of AM251. These findings suggest that circulating leptin, but not endocannabinoids, act as a modulator that tonically affects basal sweet sensitivity of lean control mice and that enhanced sweet taste responses in *db*/*db* mice may occur through tonical activation of CB_1 by endocannabinoids.

5. Conclusions

Sweet taste sensitivity has much contribution to food intake of animals. Therefore the control of sweet taste sensitivity may be one of means for regulating food (energy) intake. This paper demonstrates that leptin and endocannabinois may play important roles for regulation of peripheral sweet taste sensitivity in addition to their central actions for regulation of food intake. However, molecular mechanism how leptin and endocannabinoids affect sweet taste sensitivity is still unknown. Recent studies demonstrated that sweet taste receptors were expressed not only in taste cells but also in gastrointestinal enteroendocrine cells [60] and in pancreatic β cells [61]. Leptin and endocannabinoids may also modulate sweet sensitivity of these cells that are important for the absorption of nutrients and regulation of energy metabolism. Thus, leptin and endocannabinoids may affect energy homeostasis by regulating sweet sensitivity in various peripheral organs. These concerns would be addressed by future studies.

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