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IMPACT OF CALCIUM SIGNALING IN CARDIAC AND LIPID-TASTING CELLS: TOWARD AN INTEGRATED UNDERSTANDING OF GENETIC, METABOLIC, AND BEHAVIORAL MECHANISMS ASSOCIATED WITH OBESITY

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ABSTRACT

The concept of the "calcium clock" is particularly applied to cardiac cells where rhythmic responses that rely on fast cycles of calcium release and reuptake, with minimal reliance on STIM/Orai. But it is interesting to see to what extent this concept could also apply to lipid taste cells where sustained calcium support through SOCE is critical for maintaining the ability to detect lipids, facilitated by STIM and Orai. In lipid taste cells, there is no true "calcium clock" comparable to that of cardiac pacemaker cells, because taste cells do not generate autonomous rhythmic depolarizations or action potentials on a regular basis. However, transient calcium oscillations can be observed in response to repeated or prolonged lipid stimulation. These oscillations are largely supported by the SOCE mechanism (involvement of STIM and Orai) and by calcium release via IP3 receptors, but they do not form an involved "clock" capable of generating an autonomous rhythm. . In other words, although calcium is repeatedly mobilized in taste cells in response to fatty acids, these cells do not depend on autonomous calcium fluctuations for their function. Calcium regulation in lipid taste cells is stimulated by an external signal (the presence of fatty acids), whereas the "calcium clock" of cardiac cells is self-sustaining and motivated. Although lipid taste cells do not have an autonomous calcium clock, they exhibit a form of adaptive calcium regulation, particularly in response to repeated or prolonged exposure to dietary lipids. This adaptive regulation relies on calcium plasticity, where adjustments in intracellular calcium via STIM/Orai and IP3 maintain sensitivity to lipid stimuli despite changes in dietary fatty acid load. This process could be compared to an "adaptive calcium clock", although it does not meet the criteria of a "calcium clock" in the strict sense. Adaptive calcium regulation may emerge as a compensatory mechanism, where gustatory cells adjust their signaling in response to chronic and elevated fat intake, potentially leading to habituation. In response to ER stress, gustatory cells might upregulate STIM and Orai signaling to counter chronic calcium depletion. This adaptation could alter lipid taste sensitivity and influence eating behaviors by increasing the appetite for fatty foods.

KEYWORDS: Cardiac cells, Lipid-Tasting cells, Genetic Behavioral, Metabolic Behavioral.

INTRODUCTION

Obesity is a multifaceted global health issue, influenced by genetic predispositions, environmental factors, and dietary behaviors. Central to understanding its underlying mechanisms is the concept of the calcium clock, a well-established regulator of rhythmic calcium signaling in cardiac cells, now being explored for its potential role in other cell types, including lipid-sensitive gustatory cells (Maltsev *et al*., 2007). In cardiac cells, the calcium clock orchestrates rhythmic calcium oscillations to regulate heart rate and contraction (Lakatta & DiFrancesco, 2009). By analogy, similar calcium dynamics in gustatory cells could provide insights into the regulation of lipid perception and dietary behaviors. Calcium signaling in these cells, mediated by key proteins such as STIM, Orai, and CD36, is crucial for detecting dietary fats and transmitting gustatory signals to the brain. Dysregulation of these pathways—potentially driven by genetic or environmental factors—could alter fat taste perception, leading to overeating and the development of obesity (Cai *et al*; 2012; Maus *et al*., 2017).

By leveraging the calcium clock concept, researchers can explore how calcium oscillations and their regulatory mechanisms influence lipid sensitivity and metabolic outcomes. Advances in genetic engineering and omics technologies enable the study of calcium-related genes and their impact on fat taste sensitivity and metabolism. This translational approach has the potential to uncover causal links between calcium signaling dysfunction, dietary preferences, and obesity, offering novel targets for intervention.

This article examines the role of the calcium clock in gustatory cells, exploring its relevance to fat perception and appetite regulation. By integrating insights from genetic models and omics data, we aim to highlight how calcium clock dysregulation may contribute to obesity and propose strategies for addressing this pervasive metabolic disorder.

1. Calcium Signaling

Calcium Signaling is an essential intracellular communication mechanism that plays a pivotal role in numerous biological functions. It relies on calcium ions (Ca^{2+}) as second messengers to transmit and modulate signals within cells in response to various extracellular stimuli. This dynamic process involves multiple steps, each critical for ensuring cellular responses are precise and well-coordinated. Below are the key aspects of calcium Signaling , (i) Calcium Mobilization, Intracellular calcium is primarily stored in organelles such as the endoplasmic reticulum (ER) or mitochondria. Upon receiving a signal (e.g., a neurotransmitter, hormone, or physical stimulus), calcium is released into the cytosol, leading to an increase in its concentration. (ii) Channels and Receptors, Specific channels, such as voltage-gated calcium channels and IP_3 (inositol triphosphate) receptors located on the ER, facilitate the release and regulation of cytosolic calcium. Other channels, like ryanodine receptors, are particularly important in specialized cells such as muscle cells. (iii) Downstream Effects, Once in the cytosol, calcium binds to regulatory proteins such as calmodulin, triggering the activation of various enzymes and protein kinases. These molecular interactions regulate processes including muscle contraction, neurotransmitter release, metabolic control, and gene expression. (iv) Return to Baseline,; To restore intracellular calcium to resting levels, specialized calcium pumps (e.g., SERCA pumps in the ER and PMCA pumps in the plasma membrane) actively transport calcium out of the cytosol, either sequestering it within organelles or expelling it from the cell (Berridge *et al*. 2000).

2. Taste Perception in Gustatory Cells: A Calcium Signaling Paradigm

Calcium Signaling in gustatory cells transforms the interaction with taste molecules into an electrical signal, subsequently converted into a chemical message that conveys taste information to the brain. While the Signaling cascade varies depending on the type of taste, calcium remains a central second messenger essential for this sensory transduction process. Taste perception in gustatory cells exemplifies the fascinating role of calcium Signaling , where calcium plays a pivotal role in transmitting taste receptor signals to the brain. Here's how this process unfolds for different types of tastes:

- **Taste Detection:** Gustatory cells, located on the tongue's taste buds, detect various flavors (sweet, salty, sour, bitter, umami) through specific receptors. Depending on the type of taste, these receptors are either G protein-coupled receptors (for sweet, bitter, and umami) or direct ion channels (for salty and sour) (El-Yassimi et al., 2009).
- **Receptor Activation and Calcium Signaling:** For sweet, bitter, and umami tastes, receptor activation triggers an intracellular Signaling cascade involving specific G proteins, such as gustducin. This cascade leads to the production of second messengers like inositol triphosphate (IP3). IP3 binds to IP3 receptors on the endoplasmic reticulum, causing the release of stored calcium into the cytosol (Boughter *et al*., 1997; Berridge, 1984).
- **Cytosolic Calcium Increase:** The release of calcium into the cytosol temporarily raises its concentration, leading to depolarization of the gustatory cell membrane. This depolarization can also open voltage-gated calcium channels on the plasma membrane, allowing additional calcium influx into the cell (El-Yassimi et al., 2009).
- **Neurotransmitter Release:** The rise in intracellular calcium triggers the release of neurotransmitters, such as ATP, into the synaptic cleft near nerve fibers connected to gustatory cells. ATP acts as a chemical signal to activate gustatory nerves, which relay the information to the brain (El-Yassimi et al., 2009).
- **Signal Transmission to the Brain:** Nerve signals from gustatory cells travel via cranial nerves to the brain, where the information is processed and perceived as a specific flavor (Khan *et al*. 1996).

This highly regulated mechanism is central to cellular physiology, allowing cells to adapt to environmental changes and respond to diverse stimuli by orchestrating precise functional outcomes. Aberrations in calcium Signaling are linked to a range of diseases, including neurodegenerative disorders, cardiac conditions, and metabolic syndromes, underscoring its importance in maintaining cellular and systemic health.

3. Calcium Signaling in Lipid-Sensitive Gustatory Cells

Lipid-sensitive gustatory cells express specific receptors called CD36 (or "fatty acid receptor"). CD36 is a surface protein capable of binding fatty acids and initiating intracellular Signaling cascades. This receptor is abundant in lipid-sensitive taste cells and plays a key role in the gustatory response to lipid molecules (Wang *et al*., 2012). Puebla *et al.* (2022) have reported that Free fatty acid receptors (FFARs) and CD36 are activated by different fatty acid, such as SCFAs, MCFAs and LCFAs.

When free fatty acids bind to CD36 receptors, a cascade of signals is triggered, leading to an increase in intracellular calcium levels. This increase occurs through two main mechanisms: Calcium influx from the extracellular environment via calcium channels activated by initial Signaling and Calcium release from intracellular stores in the endoplasmic reticulum (ER), mediated by second messengers such as inositol triphosphate (IP_3) (Dramane, *et al*. (2012). Calcium depletion in lipid-sensitive taste cells refers to the reduction of calcium reserves in the ER due to sustained or excessive

activation of fatty acid-related Signaling pathways. This depletion may occur under conditions such as chronic lipid consumption or metabolic dysfunctions like obesity. Consequences of ER calcium depletion include:

Reduced sensitivity of taste cells to calcium signals, diminishing lipid taste perception and Weakened response to fatty acids, potentially altering the taste perception of fatty foods. We have previously shown this coupling of calcium phenomena (Dramane, *et al*. (2012). Calcium depletion in lipid-sensitive gustatory cells can have significant effects on taste signaling and dietary behavior. Diminished calcium Signaling may result in weaker sensory Signaling for fatty foods, influencing preferences. These cells influence reward and satiety circuits, and their dysfunction could lead to overeating of fatty foods, contributing to obesity. Gustatory cells send signals to brain centers regulating appetite and reward. Calcium Signaling dysfunction could therefore disrupt dietary behaviors and contribute to metabolic disorders (Raybould, 2007).

4. Calcium Signaling in Other Physiological Mechanisms

Calcium Signaling extends far beyond taste perception, playing a critical role in numerous physiological processes. Here are some key examples where calcium is indispensable.

- **Muscle Contraction:** Skeletal, cardiac, and smooth muscles rely on calcium for contraction. An action potential reaching a muscle cell triggers calcium release from the sarcoplasmic reticulum. In skeletal and cardiac muscles, calcium binds to troponin, allowing actin and myosin filaments to interact, resulting in contraction. Once calcium is pumped back into the sarcoplasmic reticulum, the muscle relaxes (Berridge *et al*., 2003).
- **Neurotransmitter Release:** In neurons, calcium influx occurs through voltage-gated calcium channels in response to an action potential. Elevated calcium levels in the presynaptic terminal trigger the fusion of neurotransmitter-filled vesicles with the membrane, releasing their contents into the synaptic cleft. These neurotransmitters activate postsynaptic neurons, enabling neural signal transmission (Minor, 2012; Berridge, 1998; Futatsugi *et al*., 2005).
- **Fertilization and Embryo Activation:** During fertilization, the sperm entry into the oocyte triggers a massive calcium release, known as the calcium wave. This rapid calcium surge activates the fertilized oocyte, initiating cell division and early embryonic development (Swann, 2016).
- **Hormone Secretion:** Calcium Signaling is essential in endocrine cells for hormone release. For example, in pancreatic beta cells, increased intracellular calcium levels in response to glucose stimulate insulin secretion. Similarly, in the parathyroid glands, calcium levels regulate the secretion of parathyroid hormone, which maintains blood calcium balance (Stojilkovic & Catt, (1992).
- **Apoptosis (Programmed Cell Death):** Abnormal calcium accumulation in the cytosol or mitochondria can trigger apoptosis. Calcium activates apoptotic pathways, including caspases, which break down cellular components for controlled cell death. This process is vital for tissue homeostasis and normal development (Orrenius *et al*., 2003).
- **Immunity and Lymphocyte Activation:** Calcium Signaling is critical for activating T lymphocytes during immune responses. Upon recognizing an antigen, T cells experience a rise in intracellular calcium levels. This activates downstream pathways, such as calcineurin, which facilitates transcription of cytokine-related genes and promotes T-cell proliferation (Feske *et al*., 2015).
- **Bone Homeostasis:** Calcium is essential for bone remodeling, balancing resorption by osteoclasts and formation by osteoblasts. Calcium Signaling influences the activity and differentiation of these cells. Extracellular calcium levels are tightly regulated by hormones like parathyroid hormone, calcitonin, and vitamin D to maintain bone strength (Karsenty & Wagner, 2002).

From muscle contraction to immune activation and embryonic development, calcium Signaling is a cornerstone of physiological processes. Its role as a versatile second messenger ensures precise regulation and coordination across diverse cellular systems, highlighting its fundamental importance in maintaining health and homeostasis (Berridge *et al*., 2000). Calcium Signaling is therefore essential for the functioning and regulation of numerous biological processes. Its role as a second messenger allows it to swiftly modulate various cellular responses, making this system indispensable to human physiology.

5. Calcium Signaling in Cardiac Cells: A Critical Mechanism for Heart Function

Calcium Signaling in cardiac cells is a finely orchestrated process, ensuring synchronized contraction and relaxation of cardiomyocytes. This precise regulation is crucial for effective pumping of blood and for meeting the metabolic demands of the body.

The process begins with an action potential, which propagates along the membrane of cardiomyocytes. This action potential originates in the sinoatrial node of the heart and spreads through the myocardium, coordinating cardiac contraction. As the action potential reaches the plasma membrane (sarcolemma) of cardiomyocytes, it triggers the opening of L-type voltage-gated calcium channels (Bers, 2002).

These channels allow a small influx of calcium from the extracellular environment into the cytoplasm, initiating the next steps. The initial calcium influx acts as a "trigger" for the release of stored calcium from the sarcoplasmic reticulum (SR). Calcium binds to ryanodine receptors (RyR2) on the SR, causing a large release of calcium into the cytoplasm. This process, known as excitation-contraction coupling, amplifies the calcium signal. The rise in cytoplasmic calcium enables calcium to bind to troponin C on the actin filaments. This binding alters the structure of the troponin complex, exposing myosin-binding sites on actin filaments. Actin and myosin filaments slide past one another, generating the force required for contraction. This mechanism underlies the heart's ability to contract and pump blood effectively. To relax and prepare for the next contraction, cytoplasmic calcium levels must decrease rapidly. This is achieved by SERCA Pumps (Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase). These pumps return a significant portion of calcium to the SR for storage. Na^+/Ca^{2+} Exchanger (NCX) action expels calcium from the cell by leveraging the sodium gradient. A smaller fraction of calcium is removed via Plasma Membrane Ca^{2+}-ATPase (PMCA) pump, playing a secondary role (Periasamy & Kalyanasundaram, 2007).

The autonomic nervous system fine-tunes calcium Signaling in cardiomyocytes to adjust heart rate and contraction strength based on the body's needs. Adrenaline and noradrenaline, acting through beta-adrenergic receptors, enhance calcium Signaling by increasing intracellular calcium levels, enabling stronger and faster contractions during stress or exercise (Bers, 2002).

Dysregulation of calcium Signaling can result in Arrhythmias, Abnormal calcium release can cause irregular heartbeats, Heart Failure, Impaired calcium regulation reduces contraction strength, compromising heart function and Cardiomyopathies, Mutations in ryanodine receptors or SERCA pumps can disrupt calcium homeostasis, leading to structural and functional heart defects.

Both cardiac and lipid-sensitive gustatory cells use the SERCA pump (Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase) to pump calcium back into the ER after release, maintaining cytosolic calcium levels and replenishing ER calcium stores.

In cardiomyocytes, rapid calcium reuptake is essential for muscle relaxation and preparing the cell for the next contraction (Periasamy & Kalyanasundaram, 2007).

In gustatory cells, the SERCA pump restores ER calcium levels after lipid detection, ensuring readiness for subsequent fatty acid detection (Iguchi et al., 2011).

6. Differences in Calcium Signaling Between Cardiac and Lipid-Sensitive Gustatory Cells

The key distinction between cardiac cells and lipid-sensitive gustatory cells lies in how their endoplasmic reticulum (ER) membrane receptors interact with plasma membrane proteins, specifically STIM (stromal interaction molecule) and Orai, which are pivotal for calcium signaling specificity. STIM (Stromal Interaction Molecule) is a calcium-sensing protein located in the ER membrane. Its detects calcium depletion in the ER and undergoes a conformational change, moving to regions of the ER near the plasma membrane. Orai is a calcium channel in the plasma membrane. Coupled with activated STIM facilitate calcium influx from the extracellular environment into the cytoplasm, replenishing ER calcium stores through a mechanism known as store-operated calcium entry (SOCE) (Baumbach *et al*., 2014; Derler *et al*., 2016).

In lipid-sensitive gustatory cells, STIM and Orai play a central role in sustaining calcium signaling, especially during prolonged or repeated stimulation by dietary lipids. When fatty acids bind to receptors such as CD36, they trigger a signaling cascade that releases calcium from the ER via IP3 receptors. As ER calcium levels drop, STIM activates and couples with Orai to enable continuous calcium influx, maintaining sufficient intracellular calcium levels to support ongoing lipid detection. This mechanism ensures that lipid-sensitive gustatory cells remain responsive to lipid stimuli over extended periods, preventing rapid desensitization (Prakriya & Lewis, 2015).

In cardiac cells, calcium signaling primarily depends on the coupling of L-type voltage-gated calcium channels in the plasma membrane with ryanodine receptors (RyR2) in the ER to initiate muscle contraction. This mechanism, known as excitation-contraction coupling, underpins rhythmic contractions (Marks, 2013).

The role of STIM/Orai in cardiomyocytes is minimal under normal conditions, as contraction relies primarily on calcium influx through L-type channels and release via RyR2. However, under stress or pathological conditions (e.g., heart failure), SOCE (and thus STIM and Orai) may become more prominent to compensate for compromised ER calcium stores (Collins & Bootman, 2011).

Cardiac cells and lipid-sensitive gustatory cells differ in their reliance on the STIM/Orai mechanism. Cardiac cells excitation-contraction coupling supports rapid, rhythmic responses that rely on fast cycles of calcium release and reuptake, with minimal reliance on STIM/Orai. In lipid-Sensitive Gustatory Cells, Sustained calcium support through SOCE is critical for maintaining the ability to detect lipids, facilitated by STIM and Orai.

The concept of the "calcium clock" is particularly applied to cardiac cells where rhythmic responses that rely on fast cycles of calcium release and reuptake, with minimal reliance on STIM/Orai. But it is interesting to see to what extent

this concept could also apply to lipid taste cells where sustained calcium support through SOCE is critical for maintaining the ability to detect lipids, facilitated by STIM and Orai (Zhang et al., 2003).

Let's explore the role of the "calcium clock" in both cell types and see if lipid taste cells could make use of it in a similar way.

7. The Concept of the "Calcium Clock" in Cardiac Cells and Potential Parallels in Lipid-Sensitive Gustatory Cells

In cardiomyocytes, particularly in the cells of the sinus node (the pacemaker cells of the heart), the calcium clock is a triggered oscillation of calcium in the sarcoplasmic reticulum (SR) that contributes to the triggering of action potentials, responsible for the heart rate (Berridge et al., 2000). This mechanism is based on a cyclic release of calcium by ryanodine receptors (RyR2) in the SR, which increases the intracellular calcium concentration (Van Petegem, 2015). This release leads to rhythmic calcium oscillations that activate ion channels in the plasma membrane and trigger membrane depolarizations. The calcium clock works in synergy with a membrane clock; both regulate spontaneous depolarizations, allowing fine control of the heart rate. The calcium clock is therefore essential for the automatic rhythm of the heart, acting on external nervous influences.

In lipid taste cells, there is no true "calcium clock" comparable to that of cardiac pacemaker cells, because taste cells do not generate autonomous rhythmic depolarizations or action potentials on a regular basis (Berridge et al., 2000). However, transient calcium oscillations can be observed in response to repeated or prolonged lipid stimulation. These oscillations are largely supported by the SOCE mechanism (involvement of STIM and Orai) and by calcium release via IP_3 receptors, but they do not form an involved "clock" capable of generating an autonomous rhythm. In other words, although calcium is repeatedly mobilized in taste cells in response to fatty acids, these cells do not depend on autonomous calcium fluctuations for their function. Calcium regulation in lipid taste cells is stimulated by an external signal (the presence of fatty acids), whereas the "calcium clock" of cardiac cells is self-sustaining and motivated (Besnard *et al.*, (2016).

The calcium clock of cardiac cells is vital for maintaining a constant and uninterrupted rhythm, necessary for autonomous cardiac function. This regulation allows the heart to beat in the absence of any external influence, an essential trait for an organ that must function continuously. In taste cells, the perception of lipids does not require a continuous and autonomous oscillation. On the contrary, calcium signaling in taste cells is triggered only upon detection of lipid molecules. A "calcium clock" would therefore be useless, and even energetically costly, in these cells whose activity is intermittent and dependent on food (Maltsev *et al*., 2007).

8. Broader concept of the "calcium clock": an adaptive calcium clock?

Although lipid taste cells do not have an autonomous calcium clock, they exhibit a form of adaptive calcium regulation, particularly in response to repeated or prolonged exposure to dietary lipids. This adaptive regulation relies on calcium plasticity, where adjustments in intracellular calcium via STIM/Orai and IP3 maintain sensitivity to lipid stimuli despite changes in dietary fatty acid load. This process could be compared to an "adaptive calcium clock", although it does not meet the criteria of a "calcium clock" in the strict sense.

It is plausible to suggest that the adaptive regulation of calcium in lipid-sensitive gustatory cells could be influenced by genetic factors associated with obesity, although the relationship is complex and multifactorial. Obesity arises from a combination of genetic predispositions, environmental factors, and dietary behaviors, and alterations in calcium regulation in gustatory cells may be an indirect consequence.

9. Adaptive Calcium Regulation in Lipid-Sensitive Gustatory Cells: Links to Obesity-Associated Genetic Factors

Certain genes associated with obesity influence metabolic pathways and cellular signaling, including calcium regulation (Bading, 2013; Song *et al*; 2019). Variants in genes involved in fatty acid storage and mobilization may indirectly impact lipid-sensitive gustatory cells (Abdoul-Azize & Khan, 2018). Genes affecting the expression of lipid receptors, such as CD36, or calcium-regulating proteins like STIM and Orai, could alter calcium sensitivity in gustatory cells (Dramane *et al.*, 2012). These genetic variations may lead to adaptive changes in calcium signaling, modifying the perception of dietary fats and potentially contributing to increased lipid consumption. Individuals genetically predisposed to obesity may exhibit changes in gustatory signaling, reducing sensitivity to dietary fats (Dramane *et al.*, 2012). Decreased sensitivity could lead to compensatory behaviors, such as consuming more fatty foods to achieve the same level of gustatory satisfaction, thereby increasing overall caloric intake (Sayed *et al*. 2015).

Adaptive calcium regulation may emerge as a compensatory mechanism, where gustatory cells adjust their signaling in response to chronic and elevated fat intake, potentially leading to habituation (Berridge *et al*., 2000). This habituation might result in a diminished ability to detect lipids, requiring higher fat concentrations to elicit the same taste response. Obesity induces epigenetic modifications that alter the expression of genes involved in metabolism and cellular signaling, including calcium-related pathways (Sayed *et al*. 2015). Hormones interact with calcium signaling pathways, increasing reliance on SOCE (mediated by STIM and Orai) to sustain gustatory responses to lipids Berridge, 1997). As a result, adaptive calcium regulation in gustatory cells could be shaped by the metabolic environment typical of obesity. Obesity is often associated with endoplasmic reticulum (ER) stress in various cell types, compromising the ER's ability to optimally store calcium (Hotamisligil, 2010). In response to ER stress, gustatory cells might upregulate STIM and Orai signaling to counter chronic calcium depletion (Abdoul-Azize & Khan, 2018). This adaptation could alter lipid taste sensitivity and influence eating behaviors by increasing the appetite for fatty foods.

10. Argument: A Translational Approach to Combating Obesity

The translational approach bridges basic scientific discoveries with practical applications to address complex health challenges like obesity. A focus on calcium signaling in specific cell types, particularly lipid-sensitive gustatory cells and cardiomyocytes, provides a unique window into the mechanisms underlying dietary behaviors and metabolic regulation (Song & Sergeev, 2012). The challenge is to determine the effects of specific genes on calcium signaling in various cell types. By targeting genes involved in calcium signaling (e.g., STIM, Orai, CD36, or calcium receptors in the ER), we can directly assess their roles in lipid taste sensitivity, fat perception, and obesity progression. For example, manipulating CD36 expression in gustatory cells can elucidate its impact on lipid detection and preference (Dramane *et al.*, 2012). A translational approach that combines genetically modified models, integrative omics, and insights into calcium signaling offers a robust framework for combating obesity. By linking genetic factors, calcium metabolism, and dietary behaviors, this strategy provides a pathway to develop early interventions, targeted therapies,

and personalized prevention strategies. Ultimately, such research can lead to transformative advancements in understanding and managing obesity and its associated metabolic disorders.

CONCLUSION

Calcium plasticity enables gustatory cells to adapt to prolonged stimulation, potentially leading to habituation to dietary lipids. This phenomenon implies that lipid-sensitive gustatory cells adjust their response threshold, requiring higher fat concentrations to trigger the same calcium response. Habituation may be exacerbated by genetic predispositions to obesity, making individuals more likely to seek out high-fat foods to adequately stimulate their gustatory cells. This desensitization of lipid receptors mirrors similar mechanisms seen in other systems exposed to chronic overstimulation. and dietary habits in individuals predisposed to obesity.

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