Sugar-sensing swodkoreceptors

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Abstract

Understanding how cells sense sugar is a fundamental question in biology and is pivotal for the evolution of life. In numerous organisms, sugar molecules constitute a primary source of energy generation. Consequently, the mechanisms governing sugar sensation in various microorganisms and animals have been experimentally elucidated. However, sugar sensation has primarily been investigated in specialized sensory cells such as taste buds, taste organs, or sensory neurons. These cells detect extracellular sugar through membrane-bound 'sugar or sweet receptors' or 'gustatory receptors'. However, in addition to these membrane receptors, sugar molecules can also be sensed via other sugar-binding non-membrane signaling proteins. Utilizing a supermarket employee analogy, I present my rationale for why glucokinase may not be the optimal glucose sensor. Additionally, to encapsulate all sugar-sensing proteins capable of detecting and signaling irrespective of their cellular location, I propose the term 'swodkoreceptor', derived from the Polish word 'Słodkie' meaning 'Sweet'. This proposal aims to facilitate the exploration of the identity and function of all swodkoreceptors for all the sugar molecules, akin to research that identified the bacterial Lac repressor as the allolactose swodkoreceptor and the Liver X receptor as one of the mammalian glucose swodkoreceptor.

Due to the priority in human interests, the glycolytic pathway (glucose metabolism) was initially a focus of early biochemical research due to its significance in the production of alcoholic beverages and its commercial value.[1,2] Nevertheless, since then, the mechanisms underlying sugar synthesis, transport, storage, metabolism and homeostasis has been extensively studied due to its role in energy production, diseases such as diabetes, and the development of real-time biosensors for measuring glucose levels in patients.[3-6]

Glycolysis has been proposed to have its origin in thermophilic archaea.[7-9] Both eubacteria and archaea possess the enzymatic ability to synthesize trehalose, with the evolutionary purpose of these molecules largely attributed to stress response mechanisms.[10] Trehalose serves as a virulence factor for bacteria and fungi in colonizing plant and animal cells, with its synthesis triggered by various stressors.[11-14] Nonetheless, owing to the significance of sugar, the identification of gustatory sugar receptors responsible for sugar sensing has been addressed in numerous organisms.[15-17] The trehalose-sensing gustatory receptor in Drosophila was identified as the G protein-coupled receptor Gr5a, whereas Gr5a, Gr64a, and Gr64f are among the gustatory receptors identified for other sugars such as sucrose and maltose.[18-20] In silkworm *Bombyx mori*, D-fructose is sensed by an ionotropic gustatory receptor known as Gr9, while in Drosophila, it is sensed by the ionotropic gustatory receptor Gr43a.[21] Drosophila Gr64a has also been identified as a receptor for D-fructose in the brain, enabling the sensing of D-fructose in the hemolymph.[22] In humans and mice, taste-specific G protein-coupled receptors T1R2/T1R3 have been identified and reported as the "only sweet taste receptor".[23-25] However, in fish, while grass carp T1R2s can sense sugar, zebrafish and medaka rely largely on T1R1/3 and T1R2/3 for amino acid sensing.[26-28] In mice, while glucose sensing was initially attributed to POMC (pro-opiomelanocortin) neurons, it has been reported that adhesion G-protein coupled receptor 1 (ADGRL1) functions as the glucose-sensing receptor in the ventromedial nucleus of the hypothalamus.[29,29-31]

All the aforementioned studies on gustatory sweet taste receptors focus on receptors expressed in sensory cells. However, the sensing of sugar is not confined solely to sensory cells or at the plasma membrane level. This capacity offers a specific advantage to the organism or cell, enabling it to detect sugar in its environment or blood or hemolymph and respond accordingly. The mechanism by which mammalian cells sense sugar molecules within their intracellular environment remains largely unexplored. To illustrate, consider the analogy of the month preceding Christmas Eve. The number of trucks loaded with candies waiting outside a supermarket doesn't determine the availability of candies for sale inside.

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What truly matters is the quantity of candies already inside the supermarket, ready to be sold to customers who are shopping within. Even candies waiting to be unwrapped from their delivery boxes are not sufficient. If customers cannot find readily available candies, they may choose to shop elsewhere or request assistance from salespersons to open the boxes. In more extreme cases, impatient customers, such as parents with highly demanding young children, may even take matters into their own hands and open the wrapped delivery boxes themselves.

Moreover, some animals, such as domestic cats, cannot even sense sweetness due to pseudogenization of one of the gustatory sweet receptors.[32] Does this imply that all sugar sensing in domestic cats occurs solely in the pancreas and the brain? However, even the identity of glucose-sensing receptors in the pancreas is subject to debate, as glucokinase has been suggested as the 'glucose sensor'.[33–36] Returning to our analogy, if one employee in the supermarket must serve as a 'candy sensor' or 'candy receptor', their role would be solely to monitor candy stock levels and take action if stock is low, either by receiving candy from trucks outside, unwrapping delivery crates or signaling to other employees to act. In contrast, the function of glucokinase is to catalyze the first step in glucose metabolism.[2,37] The supermarket employee's responsibility would be limited to checking candy stocks, without involvement in labeling candies for disposal or engaging in unrelated tasks like playing 'candy crush' during peak demand periods such as Christmas.

Since the majority of animal cells utilize glucose for energy production, or other microorganisms may employ sugar molecules like trehalose for stress response, it's logical to assume that cells and microorganisms possess mechanisms to sense sugar within their cytoplasm or organelles where such sugar molecules can be found. This raises the question of whether there are other sugar-sensing receptors and if they have already been identified. A promising candidate for such a sugar-sensing receptor is the nuclear receptor Liver X receptor (LXR), a transcription factor well-known for its role as an oxysterol-sensing.[38,39] In addition to its role in regulating genes related to cholesterol and fatty acid metabolism through oxysterol binding, LXR has also been reported to function as a glucose sensor. The binding of D-glucose and D-glucose-6-phosphate at physiological concentrations can stimulate the transcriptional activity of both LXR-α and LXR-β.[40] In my view, besides the term 'glucose sensor' used by the authors to describe LXR, alternative terms such as 'glucose-sensing receptor,' 'glucoreceptor,' 'sweet-sensing receptor,' or 'sweet receptor' could also be applicable to LXR. However, it may not be suitable to refer to LXR as a 'sweet taste

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receptor' or a 'gustatory receptor,' as these terms typically denote receptors specifically involved in taste perception rather than intracellular sensing of sugars.

It seems there's a lack of unity in the sugar-sensing scientific literature regarding the terms 'sweet receptor', 'sweet taste receptor', and 'sugar receptor', which are often used interchangeably. Additionally, there's a division between the use of the terms 'sensor' and 'receptor.' In my recent proposal of gasoreceptors, I have emphasized the challenges associated with this lack of consistency, drawing parallels to the blind men and the elephant parable.[41-43] It appears that in the context of estrogen- or vitamin D-sensing transcription factors, they are commonly referred to as 'receptors'. However, when it comes to gases like oxygen or sugars such as glucose, the term 'sensor' is often utilized.[38,44] Therefore, to consolidate all sugar-sensing proteins under a unified term, I propose the term "swodkoreceptor" (derived from "Słodkie," meaning "Sweet" in Polish). Embracing the concept of swodkoreceptor will facilitate the identification of receptors akin to LXR in every microorganism and within every cell of organisms.

The term 'swodkoreceptor' will encompass all subclasses of sugar/sweet/gustatory receptors, including trehalose receptors, fructose receptors, mannitol receptors, sucrose receptors, galactose receptors, lactose receptors, maltose receptors, and so forth. Identifying the roles and identities of swodkoreceptors may provide insights into the etiology of diseases related to diabetes and/or immune systems. The bacterial lac repressor (LacI) is simply a swodkoreceptor for allolactose.[45] Similarly, just as β-galactosidase is necessary for the conversion of lactose to allolactose (via transgalactosylation), which is then sensed by the LacI swodkoreceptor, the activity of glucokinase in glucose conversion might also fulfill a comparable role.[46] Therefore, the role of glucokinase in glucose sensing may simply be upstream to swodkoreceptors such as LXR, which have the capability to sense glucose-6-phosphate.[40,47]

Finally, based on their capacity for glucose-binding and potential additional roles, putative glucose swodkoreceptors may encompass proteins such as Metalloprotease TRABD2B (TraB Domain Containing 2B/TIKI2) and transcription factors like ZNF737 (Zinc Finger Protein 737).[48]

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CONFLICT OF INTEREST

None.

DISCLOSURE

The author used ChatGPT for correcting the scientific English. The author takes full responsibility for the content of this manuscript.

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