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THE CONCENTRATION/RESPONSE FUNCTION BEHAVIORSOF NONCALORIC AND CALORIC SWEETENERS

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ABSTRACT: Sweeteners are generally described in terms of their sweetness potencies relative to sucrose references. And, while caloric sweeteners have been found to have potencies invariant with sucrose reference concentration, noncaloric sweeteners decrease in potency as sucrose reference concentration increases. In this study, we develop methodology to determine the Concentration/Response functions for 9 (Omit "the") noncaloric and 2 caloric sweeteners in water at room temperature. Two-Alternative Forced Choice methodology with a panel of 80 subjects was used to determine is sweet concentrations for these 11 sweeteners and multiple concentrations of sucrose. We found that the is sweetness data for all 8 of the high-potency noncaloric sweeteners are well modeled by the Law of Mass Action $R = (R_m X C)/(K_d + C)$, where R is Response in % Sucrose Equivalents, R_m is Maximal Response in % Sucrose Equivalents, C is the sweetener Concentration in mg/L and K_d is the Concentration in mg/L resulting in Half-Maximal Response. We also found that the is sweetness data for the 2 caloric sweeteners Glucose and Fructose as well as the noncaloric sweetener Erythritol are well modeled by the linear function $R = mC + b$ where m is the sweetener potency. This study enables an improved understanding of the bio-rationale for the well-known phenomenon of Sweetness Linger for high-potency noncaloric sweeteners. The K_d values determined for these sweeteners enable calculation of the half-lives for Sweetener Receptor / Sweetener dissociation. Our results make it clear that prolonged residence time on the Sweetener Receptor cannot be the bio-rationale for Sweetness Linger.

INTRODUCTION: Sucrose is the consumer's standard for quality of sweet taste and, in the food and beverage industry, we attempt to replicate it in both caloric and non-caloric sweetener systems. High Fructose Starch Syrup (HFSS) sweeteners are predominantly mixtures of Fructose (FRU) and Glucose (GLU) and HFSS-42 (42% FRU) and HFSS-55 (55% FRU) are very common caloric sucrose alternatives.

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The 6 synthetic noncaloric sweeteners Acesulfame-K (ACE-K), Aspartame (APM), Cyclamate-Na (CYC-Na), Neotame (NTM), Saccharin-Na (SAC-Na) and Sucralose (SUL) are the most commonly used synthetic noncaloric sweeteners and the 3 natural noncaloric sweeteners Rebaudioside A (REBA), Rebaudioside M (REBM) and Erythritol (ERY) are commonly used natural noncaloric sweeteners.

In this report, we describe an improved method for the determination of C/R functions for these 11 sweeteners in water at neutral pH. In earlier work, a Descriptive Analysis Panel was employed to determine C/R functions for some of the sweeteners included in this study and the results

obtained in this early study are provided in **Table 1** [1]. In this work, panelists rated the sweetness intensities of the sweetener solutions on a scale of 0 -15 where these numbers represented the sweetness intensities of 0 - 15% sucrose. On plotting the data from this experimentation, it was apparent that the data for high-potency noncaloric sweeteners are hyperbolic and can be modeled by the function $R = (R_m \text{ X } C)/(K_d + C)$, a common form of the Law of Mass Action for modeling the activities of drugs acting at their receptors [2]. Interestingly, however, the C/R data for the carbohydrate caloric sweeteners FRU and GLU were not well modeled by this hyperbolic function, but rather by a linear function. At the time this work was done in the late 1980s, it was generally believed that sweetness was mediated by multiple receptors and, further, that single receptors may have multiple binding sites for some sweeteners, just as hemoglobin has multiple binding sites for oxygen [3].

These oxygen binding sites on hemoglobin exhibit positive cooperativity with each other such that binding of the second oxygen molecule is enhanced relative to the first oxygen molecule to bind. This phenomenon of positive cooperativity in oxygen/hemoglobin binding was explained by Hill in 1910 and led to a variant of the Mass Action Equation known as the Hill equation $R = (R_m \text{ X } C^n)/(K_d^n + C^n)$ now used to explain cooperativity in the binding of some drugs to their receptors [4].

Based on the assumption that, for some high-potency sweeteners, more than one sweetener molecule may bind to a single receptor, data for the high-potency sweeteners in this study were fit to the Hill equation, where the exponent n is known as the Hill coefficient. Thus, for the noncaloric sweeteners SUL, SAC-Na and CYC-Na, the data was best modeled for values of $n > 1$ suggesting that they act at a sweetener receptor with multiple binding sites for these sweeteners which exhibit positive cooperativity. On the other hand, the data for the noncaloric sweeteners APM, ACE-K and REBA were best modeled for $n = 1.0$ as would be expected for a sweetener receptor for these sweeteners which has a single binding site for each of them. However, later as a result of the work of Li and coworkers at Senomyx in 2002 [5], we now know that human sweetness is mediated by a single heterodimeric G Protein Coupled Receptor (GPCR) known as TASR2/TASR3 and that this receptor contains at least 6 loci where sweeteners of different structural classes bind [6]. It is probable that cooperativity exists between these different sweetener binding sites, thus explaining the phenomenon of sweetness synergy, but unlikely that single sweeteners bind to more than one site on TASR1/TASR2.

TABLE 1: C/R FUNCTIONS OF SWEETENERS IN WATER AT AMBIENT TEMPERATURE BY DESCRIPTIVE ANALYSIS

Sweetener	C/R Function
GLU	$0.60C + 0.04$
FRU	$1.27C – 0.02$
ACE-K	$R = 11.6C/(470 + C)$
APM	$R = 16.0C/(560 + C)$
CYC-Na	$R = 11.3C^{1.8}/(1800^{1.8} + C^{1.8})$
REBA	$R = 10.0C/(200+C)$
SAC-Na	$R = 9.0C^{1.4}/(96^{1.4} + C^{1.4})$
SUL	$R = 13.0C^{1.4}/(110^{1.4}+C^{1.4})$

In the course of the research leading to the C/R functions in **Table 1**, it was recognized that the equations generally predict sweetener concentrations that are high as matches for specific sucrose concentrations. For example, the APM C/R function predicts that the concentration equivalent in sweetness to 10% sucrose to be 930mg/L. However, commercial beverages are generally formulated to be comparable in sweetness intensity to 10% sucrose and the APM concentrations in these beverages are typically ca. 500mg/L. The Descriptive Analysis Panel work that led to the C/R functions in **Table 1** only allowed panelists to rate the sweetness intensities of sweetener solutions on a scale of 0-15. A problem with this methodology is that it can cause "end of scale" effects as no concentration of any sweetener can be rated higher than 15 (i.e., 15% sucrose equivalency). An attempt was made to correct this problem for APM allowing panelist ratings from 0 – 16, thereby yielding the equation given in **Table 1** where $R_m = 16.0$. However, it is apparent that this protocol adjustment still greatly over-predicts the 10% sucrose equivalent concentration of APM. In recognition of the inaccuracies of the existing non-caloric sweetener C/R functions, other methods were considered for generation of C/R functions. Discrimination Testing is generally accepted as the most accurate method of determination of iso-sweetness points in comparisons of sweeteners [7]. And a preliminary study was carried out with APM

and SAC-Na using 2-Alternative Forced Choice (2-AFC) Difference Testing methodology. As in the earlier Descriptive Analysis Panel C/R function work, the data from this preliminary study was found to be well modeled by the Law of Mass Action. In this case, however, since the structure of the human sweetener receptor is now known and since it is highly unlikely that the receptor has more than a single binding site for each sweetener, the simpler function $R = (R_m \text{ X } C)/(K_d + C)$ was used. The new C/R functions based on data from 2-AFC issweetness determinations were found to predict APM and SAC-Na concentrations as expected from typical use levels in commercial beverages. And, given these initial promising results, we determined C/R functions for all of the caloric and noncaloric sweeteners of current commercial significance FRU, GLU, ACE-K, APM, CYC-Na, NTM, SAC-Na, SUL, REBA, REBM and ERY in water at neutral pH and ambient temperature (20-23°C).

MATERIAL AND METHODS: Chemicals used in this study were obtained from internal sources at The Coca-Cola Company or were purchased from commercial suppliers. A difference testing sensory panel of 80 screened employees was used to determine issweetness concentrations for the 11 sweeteners studied and least squares regression analysis was used for determination of the C/R functions. Details are as follows:

Chemicals: The 75% H_3PO_4, citric acid and tribasic potassium citrate were obtained from The Coca-Cola Company Atlanta Beverage Base Plant (Atlanta, GA). Other chemicals employed in this study were as follows: Sucrose (Domino Sugars®, Baltimore, MD), Erythritol (Cargill, Minneapolis, MN), Aspartame and Neotame (The NutraSweet Company Chicago, IL), Acesulfame-K (Celanese, Frankfurt, Germany), Sucralose (McNeil Nutritionals, LLC, Fort Washington, PA), Sodium Saccharin (CRI, S Korea), Sodium Cyclamate (Brasfanta, Hong Kong), Rebaudioside A (Cambrex, Charles City, Inc., Charles City, IA), Rebaudioside M (PureCircle, Malaysia) and Potassium Benzoate (The Specialty Chemicals Innovator, Kalama, WA) and Carbon-treated (CT) water was used in preparation of all samples.

Sensory Analysis: The sucrose solutions used for isosweetness determinations for the 11 sweeteners studied are given in **Table 2**. For each sweetener, at each sucrose matching concentration, it was necessary to estimate the isosweet concentration of the sweetener. This was done by 2-3 experienced people. And then 4 solutions of the sweetener at 70, 85, 115 and 130% or 5 solutions of the sweetener at concentrations of of 70, 85, 100, 115 and 130% of this concentration were prepared for the 2-AFC testing by the 80 person panel. After the data was collected from the panel, the data was plotted (Ordinate Axis: % of Subjects Selecting Sweetener Samples as Sweeter; Abscissa Axis: Sweetener Concentration) and determine the sweetener issweetness concentration C as the sweetener concentration at which the plot crosses the 50% of subjects line. The instructions provided to the panelists were as follows:

- You will be served 5 pairs of samples, one pair at a time.
- Each time you will be asked to indicate the sweeter sample.
- There will be a 1 minute interval between each pair of samples.
- Please eat a cracker and drink some water before each pair and.
- The samples presented to you may be either caloric or noncaloric sweeteners.

TABLE 2: SWEETENERS AND SE RANGES FOR C/R FUNCTION DETERMINATIONS

Sweetener	Sucrose Iso-Sweetness Determination Points (% Sucrose)
GLU	2.00, 5.35, 8.65, 12.00
FRU	2.00, 5.35, 8.65, 12.00
APM	2.00, 4.50, 7.00, 9.50, 12.00 or 2.00, 5.35, 8.65, 12.00
ACE-K	2.00, 3.00, 4.00, 5.00, 6.00 or 2.00, 3.35, 4.65, 6.00
SUL	2.00, 4.50, 7.00, 9.50, 12.00 or 2.00, 5.35, 8.65, 12.00
NTM	2.00, 4.50, 7.00, 9.50, 12.00 or 2.00, 5.35, 8.65, 12.00
SAC-Na	2.00, 3.00, 4.00, 5.00, 6.00 or 2.00, 3.35, 4.65, 6.00
CYC-Na	2.00, 3.00, 4.00, 5.00, 6.00 or 2.00, 3.35, 4.65, 6.00
REBA	2.00, 4.50, 5.25, 6.00 or 2.00, 3.35, 4.65, 6.00
REBM	1.00, 3.60, 5.00, 6.20, 8.00
ERY	2.00, 3.00, 4.00, 5.00, 6.00 or 2.00, 3.35, 4.65, 6.00

C/R Function Determination: The C/R functions for the high-potency sweeteners were determined using PROC NLIN in SAS/STAT [8]. The form of the model used in the analysis is $R = (R_m \text{ X } C)/(K_d + C)$, where R and C are the observed values of sweet taste intensity and sweetener concentration, respectively, and R_m and K_d are the parameters in the model that are estimated for each sweetener. The C/R functions for FRU, GLU, and ERY were fit to the simple linear regression equation R = mC using PROC REG in SAS [8].

RESULTS: We found that the C/R functions for all 8 high-potency noncaloric sweeteners are hyperbolic in nature. The isosweetness data for the 8 high-potency sweeteners were fit to the equation $R = (R_m \text{ X } C)/(K_d + C)$ and the data for FRU, GLU and ERY were fit to the equation R = mC + b by simple linear regression analysis.

Generally the FRU, GLU and ERY plots did not give ordinate axis intercepts of exactly 0 and so the data was subsequently fit to the equation, R = mC, since it is intuitively obvious that the sweetness of a sweetener at C = 0 mg/L should be 0. We regard this method, which forces an ordinate intercept of 0, as the preferred method since the Law of Mass Action based C/R functions for high-potency sweeteners are also forced, by the nature of the method, through an ordinate intercept of 0. C/R function determination results are summarized in **Table 3.**

TABLE 3: SWEETENER C/R FUNCTIONS DETERMINED IN WATER

Sweetener	C/R Function
GLU	R = 0.58C
FRU	R = 1.14C
ACE-K	R = 9.3C/(304 + C)
APM	R = 25.5C/(1160 + C)
CYC-Na	R = 28.0C/(7480 + C)
ERY	R = 0.56C
NTM	R = 28.5C/(30.4 + C)
REBA	R = 8.2C/(194 + C)
REBM	R = 11.3C/(257+C)
SAC-Na	R = 9.9C/(143 + C)
SUL	R = 19.9C/(236 + C)

DISCUSSION: The linear C/R functions for the carbohydrate and polyol sweeteners FRU, GLU and ERY show that these sweeteners can provide any sweetness intensity reached by sucrose solutions, only that higher concentrations are required. On the other hand, the hyperbolic C/R functions for the 8 high-potency sweeteners show that they cannot provide very high levels of sweetness. We have determined sweetness maximal responses (R_ms) in % sucrose equivalents as well as apparent Receptor/Sweetener dissociation constants (K_ds) for these 8 sweeteners and these R_m and K_d values have practical significance affecting how these sweeteners may be used in food and beverage applications.

High-Potency Sweetener R_m Values: On inspection of the C/R functions for the different sweeteners in **Table 3**, it can be seen that there is very significant variability in R_m values. To illustrate this point, consider NTM which exhibits an R_m of 28.5, while REBA under the same conditions only exhibits an R_m of 8.2. The low R_m for REBA is not an unusual finding for high-potency sweeteners. SAC-Na (R_m = 9.9) and ACE-K (R_m = 9.3), two sweeteners of great commercial significance, also exhibit low R_m values. We can only speculate as to the reasons why some sweeteners exhibit low R_m values. Generally, in pharmacology, compounds which exhibit low maximal responses at receptors are partial agonists [9]. Thus, even at concentrations where the receptor is 100% bound to its ligand, the response elicited is only a fraction of the response elicited by another ligand. When this is the case, the reason is generally thought to be a consequence of the drug binding to both the active and inactive conformations of the receptor, where only the former can initiate signaling. Thus it could be that, while sucrose is able to cause a maximal effect as it only binds to the active receptor conformation, other sweeteners, and especially SAC-Na, ACE-K, REBA and REBM, bind to both active and inactive receptor conformations, thereby limiting the cellular response.

R_m values for high-potency sweeteners are very important for assessment of whether or not a sweetener can be used in food or beverage products as a sole sweetener or if it must be used in blends. Commercially, the most widely used high-potency sweeteners today are APM (R_m = 25.5), SAC-Na (R_m = 9.9), ACE-K (R_m = 9.3) and SUL (R_m = 19.9). Of these, it is important to note that beverages with good to acceptable taste quality have been commercialized with aspartame and sucralose as sole sweeteners, but not with SAC-Na

or ACE-K. This is because beverages generally are in the range of 9-12% sucrose equivalency and this level of sweetness intensity cannot be reached with SAC-Na or ACE-K alone, while you can do so with either APM or SUL. Thus all beverages in the marketplace which contain either SAC-Na or ACE-K are blended sweetener systems (e.g., APM/SAC-Na, APM/ACE-K, SUL/ACE-K, *etc*.). On reflection on this fact, we should expect it to be difficult to formulate a beverage with REBA (R_m = 8.2) as the sole sweetener whereas with REBM (R_m = 11.3), the situation is improved due to REBM's higher R_m.

The differences in the C/R functions which we determined employing 2-AFC methodology and the equations determined employing a Descriptive Analysis (DA) methodology merit comment. The first and most obvious difference is that, for some of the sweeteners (i.e., APM, SUL, CYC-Na and NTM), the R_m values generated by DA methodology are much lower than generated by 2-AFC methodology, while for other sweeteners (i.e., SAC-Na, ACE-K and REBA), the differences are small. For the cases of APM, CYC-Na, SUL and NTM, the R_m values obtained by 2-AFC methodology are in the range of 19.9 – 28.5 SE units, while for the cases of ACE-K, SAC-Na and REBA, the R_m values are at 8.2 – 9.9 SE units.

The reason for the low R_m values for APM, CYC-Na and SUL obtained using DA methodology is quite likely a result of the protocol constraining panelist responses to a 0 - 15 scale. Thus the protocol likely caused an "end of scale" effect inhibiting panelists in rating sample sweetness intensities at near the end of the scale. And this effect clearly explains the suppressed R_m values determined for APM, CYC-Na and SUL by DA methodology.

High-Potency Sweetener K_d Values: Regression analysis of the high-potency sweetener 2-AFC data to the equation $R = (R_m \text{ X } C)/(K_d + C)$also provides K_d values, which represent apparent receptor/sweetener dissociation constants. In the form that the equations in **Table 3** are presented, K_d values are given in units of mg/L and have the physical meaning of the sweetener concentration at which the receptor is 50% occupied. Thus, for the case of APM (K_d = 1160mg/L = 3.9mM), at 1160mg/L, the system is responding at 50% of its maximal response to APM.

It is noteworthy, however, that other GPCRs respond to agonists at much lower concentrations. For example, the apparent K_d for fentanyl at the μ-opioid receptor, also a GPCR, has been reported to be 1.23 nM [10]. Thus APM is really not a very potent sweetener at all and it may be that, in time, sweeteners as much as a million-fold more potent than APM will be found.

A major limitation of high-potency noncaloric sweeteners is their lingering sweet aftertastes causing many consumers to reject them. And it has been assumed by many that this lingering aftertaste is due to the higher affinities that high-potency sweeteners have for the sweetener receptor. Now, enabled by the 1) availability of Receptor/ Sweetener Dissociation Constants (K_ds), from the C/R functions determined in this study, 2) the fact that K_ds are the quotients of receptor/sweetener dissociation rate constants (k_ds) and receptor/sweetener association constants (k_as) and 3) the fact that the receptor sweetener association rates should be under diffusion control in the aqueous oral environment (i.e., $k_a \sim 1.5 \text{ X } 10^9 \text{ M}^{-1}\text{sec}^{-1}$) [11] we can calculate the rates constants for receptor/sweetener dissociation for the high-potency sweeteners in our study. These calculated k_d values are given in **Table 4.** And since the dissociation of the receptor/sweetener complex must be a first order reaction, the half-life ($t_{1/2}$) for receptor/sweetener binding can be calculated by the equation $t_{1/2} = \ln 2/k_d$ [12]. Thus, the sweetener/receptor binding half-lives for the 8 high-potency sweeteners in our study are calculated and provided in **Table 4.**

The most potent high-potency sweetener included in our study was NTM, where the C/R function was determined to be R = 28.5C/(30.4 + C). From this equation, it can be calculated that the NTM concentration equivalent to 10% sucrose is 16.4mg/L and thus the potency of NTM, relative to a 10% sucrose reference, is 6100. And from the results in **Table 4**, it is clear that even NTM has a very short residence time on the receptor. NTM's $t_{1/2}$ for receptor/NTM dissociation is only 5.8msec. And of course the residence times for all the other high-potency sweeteners are much shorter.

Thus, given the very short $t_{1/2}$ values determined for these sweetener/receptor complexes, it is clear that the amounts of these sweeteners still bound to the receptor after 1 minute are negligible. And we conclude that strong binding affinity for high-potency sweeteners to the sweetener receptor cannot be the bio-rationale for their lingering sweet aftertastes. Recently a rationale for the lingering sweet aftertaste of high-potency sweeteners has been proposed which is consistent with short receptor/sweetener complex dissociation times as well as all other empirical observations on sweetener lingering sweet aftertaste [13]. It is known that the lingual epithelium is covered by a 25µm thick mucin hydrogel [14]. Further, it is known that the entire alimentary system epithelia is coated with mucin hydrogels. And, it has been determined that therapeutic drugs are delayed in their bioavailability due to slowed diffusion through the mucin hydrogel in the small intestine [15]. Thus, by analogy, it was proposed that high-potency sweeteners reach the sweetener receptor more slowly than carbohydrate sweeteners due to nonspecific binding to hydrophobic sites in the mucin hydrogel and, on release from receptor binding, their diffusion away from the sweetener receptor is delayed thereby causing iterative activation of the receptor which is perceived as lingering sweet aftertaste.

TABLE 4: HALF-LIVES FOR SWEETENER RECEPTOR / RECEPTOR COMPLEX DISSOCIATION

Sweetener	K_d (mg/L)	K_d (mM)	k_d (sec^{-1} X 10^{-6})	$t_{1/2}$ (µsec)
ACE-K	304	1.51	2.27	0.31
APM	1160	3.94	5.91	0.12
CYC-Na	7482	37.19	55.8	0.012
NTM	30.4	0.08	0.12	5.8
REBA	194	0.20	0.30	2.3
REBM	257	0.20	0.30	2.3
SAC-Na	143	0.69	1.04	0.67
SUL	236	0.59	0.89	0.78

CONCLUSIONS: All 8 high-potency sweeteners showed C/R function behavior well modeled by the Law of Mass Action hyperbolic function, $R = (R_m X C)/(K_d + C)$, while the two carbohydrate and one polyol type sweeteners showed linear C/R function behavior well modeled by R = mC. The 2-AFC methodology for determination of sweetener / sucrose issweetness points provided data which led to high-potency C/R functions which predict sweetener concentrations expected from use levels of these sweeteners in commercial food and beverage products. The apparent sweetener receptor / sweetener complex dissociation constants determined in this study enable the conclusion that the increased binding affinities of the known high-potency sweeteners cannot be the rationale to explain the phenomenon of sweetness linger.

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