Advances in the Science of Sweet Taste & Sweetness Enhancement

Grant E DuBois
Research Fellow
The Coca-Cola Company
Atlanta, GA
USA

The Coca-Cola Company
I. Sensing Foods and Beverages

II. Metrics for Commercial Viability of Sweeteners and Sweetness Enhancers

III. Sweetness Modulation, aka Optimizing the Tastes of the Non-Caloric Sweeteners of Today

IV. Sweetener Receptor Positive Allosteric Modulators, a Novel Approach to Sugar-Like Taste
I. Sensing Foods & Beverages:

Gustation
Gustation: A Superimposition of 5 Taste Modalities

1. **Sweet**
2. Bitter
3. Umami
4. Salty
5. Sour
Lingual Taste Buds are Found in Papillae
What Do Taste Buds and Taste Bud Cells Look Like?


The Coca-Cola Company
What does the Sweetener Receptor Look Like and How does Sugar Activate it?

Sucrose

T₁R₂

T₁R₃
II. Metrics for Commercial Viability of Sweeteners and Sweetness Enhancers
Key Message:

In order to realize outstanding commercial success, a new sweetness technology must deliver on all of the metrics.......Safety, Taste Quality, Stability, Solubility and Cost ...... and without compromise on Safety or Taste Quality.
Commercial Viability is Dependent on 6 Metrics

1. Safety
2. Taste Quality
   • C/R Function & R_m
   • Flavor Profile
   • Temporal Profile
   • Adaptation Profile
3. Stability
4. Solubility
5. Cost
6. Patentability

III. Sweetness Modulation, aka
Optimizing the Tastes of the Non-Caloric Sweeteners of Today
Key Messages:

1. HP sweeteners known today do not match the Taste Quality of sugar……….and delivery on the Taste Quality metric requires “Sweetness Modulators”; and

2. Since trial-and-error approaches have been employed for saccharin (>100 years) and aspartame (~30 years) w/o significant progress……..a new paradigm……..a Mechanism of Action (MOA) based paradigm……..is needed to find effective “Sweetness Modulators”.

The Coca-Cola Company
“All Models are wrong. Some are useful.”

George Box
“It’s no trick to get the right answer when you have all the data. The real creative trick is to get the right answer when you have only half the data in hand and half of it is wrong. And you don’t know which half....”

Melvin Calvin
MOA Approach to Rebaudioside A Sweetness Modulators

Operating Principle: The non-sugar-like taste of REBA is intrinsically linked to its chemical structure!

Sucrose (M = 342) = REBA (M = 967)

The Coca-Cola Company
MOA Approach to Rebaudioside A Sweetness Modulators (Cont’d)

- **Maruzen Pharmaceutical Company**: NaCl found to cause a 2.5-fold increase in potency of stevia sweeteners.

- **The Coca-Cola Company**: NaCl, and/or other osmolytes, found to cause increases in sweetness potencies as well as elimination of the slow sweetness onset and the sweetness linger for Rebaudioside A and other HP sweeteners thus leading to the **Non-Specific Binding Hypothesis**.¹,²

- **Keiko Abe Laboratory (University of Tokyo)**: Support for the Non-Specific Binding Hypothesis as the rationale for slow sweetness onset and sweetness linger.³
### Rebaudioside A (500mg/L) / Osmolyte Formulations

<table>
<thead>
<tr>
<th>Osmolyte</th>
<th>Concentration (mOsM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample A</td>
</tr>
<tr>
<td>Erythritol</td>
<td></td>
</tr>
<tr>
<td>NaCl</td>
<td></td>
</tr>
<tr>
<td>KCl</td>
<td></td>
</tr>
<tr>
<td>Osmolarity (Total)</td>
<td></td>
</tr>
<tr>
<td>Sweetness Linger (0-5)</td>
<td></td>
</tr>
</tbody>
</table>
Rebaudioside A (500mg/L) / Osmolyte Formulations

<table>
<thead>
<tr>
<th>Osmolyte</th>
<th>Concentration (mOsM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample A</td>
</tr>
<tr>
<td>Erythritol</td>
<td>500</td>
</tr>
<tr>
<td>NaCl</td>
<td>0</td>
</tr>
<tr>
<td>KCl</td>
<td>0</td>
</tr>
<tr>
<td>Osmolarity (Total)</td>
<td>500</td>
</tr>
<tr>
<td>Sweetness Linger (0-5)</td>
<td>0</td>
</tr>
</tbody>
</table>
Rebaudioside A (500mg/L) / Osmolyte Formulations

<table>
<thead>
<tr>
<th>Osmolyte</th>
<th>Concentration (mOsM)</th>
<th>Sample A</th>
<th>Sample B</th>
<th>Sample C</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythritol</td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>NaCl</td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>KCl</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Osmolarity (Total)</td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Sweetness Linger</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>
Rebaudioside A (500mg/L) / Osmolyte Formulations

<table>
<thead>
<tr>
<th>Osmolyte</th>
<th>Concentration (mOsM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample A</td>
</tr>
<tr>
<td>Erythritol</td>
<td>0</td>
</tr>
<tr>
<td>NaCl</td>
<td>0</td>
</tr>
<tr>
<td>KCl</td>
<td>500</td>
</tr>
<tr>
<td>Osmolarity (Total)</td>
<td>500</td>
</tr>
<tr>
<td>Sweetness Linger (0-5)</td>
<td>0</td>
</tr>
</tbody>
</table>
IV. Sweetener Receptor Positive Allosteric Modulators (aka Sweetness Enhancers), a Novel Approach to Sugar-Like Taste at Lower Calories
Key Message:

Sweetener receptor positive allosteric modulators (PAMs)..........aka enhancers.......which potentiate the activities of carbohydrate sweeteners enable accurate reproduction of carbohydrate sweetener taste quality w/ dramatic reduction in caloric content.
Sweetener Receptor Positive Allosteric Modulators

An Early Conceptual View of the Function of a Positive Allosteric Modulator (PAM) in the Sweetener Receptor

The Coca-Cola Company
2001: @ 375 mg/L, **DHB enhances 6% sucrose to 8% sucrose w/o any off taste**! A weaker effect was noted for fructose and no effect for glucose.


The Coca-Cola Company
Senomyx Collaboration: PAM Discovery by HTS / Cell-Based Assay


The Coca-Cola Company
MOA for PAM Activity at the Sweetener Receptor


The Coca-Cola Company
What will be the Future of Sweetener Receptor PAMs?

• **Efficacy of Sweetener Receptor PAMs:** Ma et al.,* have reported GPCR PAMs w/ >100-fold enhancements. *Can 100-fold enhancers be found for the sweetener receptor?*
  

• **Agonist Specificity for Sweetener Receptor PAMs:** PAMs reported to date exhibit specificity for individual CHO sweeteners. *Can PAMs be identified which enhance all sweeteners?*

• **Natural PAMs:** PAMs reported to date are synthetic compounds which are being developed as artificial flavors. *Can commercially-viable natural enhancers be found which can be labeled as natural flavors?*

• **PAMs for Natural High-Potency Sweeteners:** PAMs for stevia sweeteners would enable their use at lower concentrations which may help address their negative taste attributes. *Can commercially-viable enhancers for stevia and other natural high-potency sweeteners be found?*
Acknowledgements

The Coca-Cola Company: Rafael San Miguel, George King, Indra Prakash, Michael Carakostas, John Clos, Valerie Mercier and Karen Wilkens

Cargill: Dirk Reif, Leslie Currie and Amy Boileau

Senomyx: Mark Zoller, Don Karanewsky, Xiaodong Li, Guy Servant, Katia Tachjdian, Tanya Ditschun, Lubert Stryer, Charles Zuker and Roger Tsien